

=> fil hcap

FILE 'HCAPLUS' ENTERED AT 11:20:23 ON 14 JUL 2005  
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FILE COVERS 1907 - 14 Jul 2005 VOL 143 ISS 3  
FILE LAST UPDATED: 13 Jul 2005 (20050713/ED)

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=> fil reg

FILE 'REGISTRY' ENTERED AT 11:20:25 ON 14 JUL 2005  
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STRUCTURE FILE UPDATES: 13 JUL 2005 HIGHEST RN 854992-86-2  
DICTIONARY FILE UPDATES: 13 JUL 2005 HIGHEST RN 854992-86-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

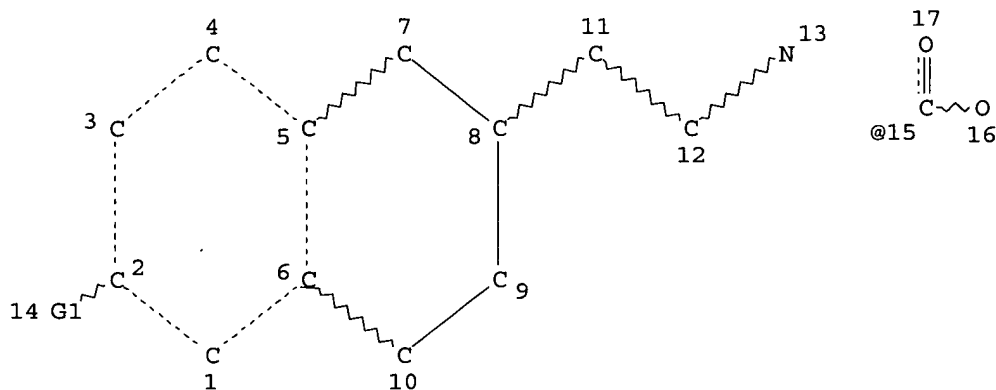
\*\*\*\*\*  
\*  
\* The CA roles and document type information have been removed from \*  
\* the IDE default display format and the ED field has been added, \*  
\* effective March 20, 2005. A new display format, IDERL, is now \*  
\* available and contains the CA role and document type information. \*  
\*  
\*\*\*\*\*

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:  
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> => d que stat 19

L1 1 SEA FILE=HCAPLUS ABB=ON PLU=ON US2003-643699/APPS  
 L3 TRANSFER PLU=ON L1 1- RN : 3 TERMS  
 L4 3 SEA FILE=REGISTRY ABB=ON PLU=ON L3  
 L6 STR



VAR G1=X/15  
 NODE ATTRIBUTES:  
 CONNECT IS E4 RC AT 8  
 DEFAULT MLEVEL IS ATOM  
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
 RING(S) ARE ISOLATED OR EMBEDDED  
 NUMBER OF NODES IS 17

STEREO ATTRIBUTES: NONE

L8 312 SEA FILE=REGISTRY SSS FUL L6  
 L9 1 SEA FILE=REGISTRY ABB=ON PLU=ON L8 AND L4

=> d iderl 19

L9 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN  
 RN 116644-53-2 REGISTRY  
 ED Entered STN: 02 Oct 1988  
 CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)  
 OTHER CA INDEX NAMES:  
 CN Acetic acid, methoxy-, 2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, (1S-cis)-  
 OTHER NAMES:  
 CN (1S,2S)-2-[2-[[3-(1H-Benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1-isopropyl-1,2,3,4-tetrahydronaphthalen-2-yl methoxyacetate  
 CN (1S,2S)-2-[2-[[3-(2-Benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate  
 CN Mibefradil  
 FS STEREOSEARCH  
 MF C29 H38 F N3 O3  
 CI COM  
 SR CA  
 LC STN Files: ADISINSIGHT, ADISNEWS, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAPLUS, CASREACT, CIN, DDFU, DIOGENES, DRUGU, IMSDRUGNEWS, IMSPATENTS,

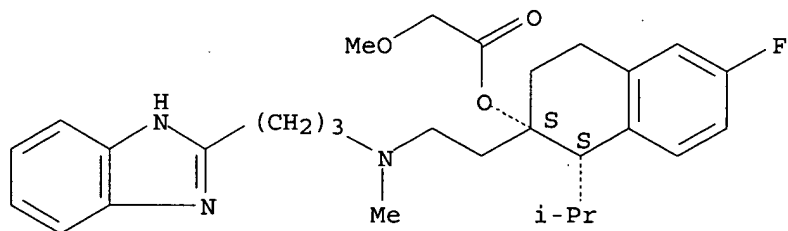
IMSRESEARCH, IPA, MEDLINE, MRCK\*, PATDPASPC, PROMT, PROUSDDR, PS,  
SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL

(\*File contains numerically searchable property data)

Other Sources: WHO

DT.CA Caplus document type: Book; Conference; Dissertation; Journal; Patent  
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC  
(Process); PRP (Properties); USES (Uses)  
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological  
study); PREP (Preparation); USES (Uses)  
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological  
study); MSC (Miscellaneous); PREP (Preparation); PROC (Process); PRP  
(Properties); USES (Uses)

Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

379 REFERENCES IN FILE CA (1907 TO DATE)

7 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

381 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file stnguide

FILE 'STNGUIDE' ENTERED AT 11:21:05 ON 14 JUL 2005

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FILE CONTAINS CURRENT INFORMATION.

LAST RELOADED: Jul 8, 2005 (20050708/UP).

=> => fil reg

FILE 'REGISTRY' ENTERED AT 14:08:35 ON 14 JUL 2005  
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STRUCTURE FILE UPDATES: 13 JUL 2005 HIGHEST RN 854992-86-2  
DICTIONARY FILE UPDATES: 13 JUL 2005 HIGHEST RN 854992-86-2

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TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

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conducting SmartSELECT searches.

\*\*\*\*\*  
\*  
\* The CA roles and document type information have been removed from \*  
\* the IDE default display format and the ED field has been added, \*  
\* effective March 20, 2005. A new display format, IDERL, is now \*  
\* available and contains the CA role and document type information. \*  
\*  
\*\*\*\*\*

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more  
information enter HELP PROP at an arrow prompt in the file or refer  
to the file summary sheet on the web at:  
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> fil lreg

FILE 'LREGISTRY' ENTERED AT 14:08:39 ON 14 JUL 2005  
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LREGISTRY IS A STATIC LEARNING FILE

NEW CAS INFORMATION USE POLICIES, ENTER HELP USAGETERMS FOR DETAILS.

=> fil zcap

FILE 'ZCAPLUS' ENTERED AT 14:08:42 ON 14 JUL 2005  
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FILE LAST UPDATED: 13 Jul 2005 (20050713/ED)

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=> fil hcap  
FILE 'HCAPLUS' ENTERED AT 14:08:44 ON 14 JUL 2005  
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FILE COVERS 1907 - 14 Jul 2005 VOL 143 ISS 3  
FILE LAST UPDATED: 13 Jul 2005 (20050713/ED)

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substance identification.

=> fil medlin  
FILE 'MEDLINE' ENTERED AT 14:08:55 ON 14 JUL 2005  
  
FILE LAST UPDATED: 13 JUL 2005 (20050713/UP). FILE COVERS 1950 TO DATE.  
  
On December 19, 2004, the 2005 MeSH terms were loaded.  
  
The MEDLINE reload for 2005 is now available. For details enter HELP  
RLOAD at an arrow prompt (=>). See also:

<http://www.nlm.nih.gov/mesh/>  
[http://www.nlm.nih.gov/pubs/techbull/nd04/nd04\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html)

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the  
MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate  
substance identification.

=> fil biosis  
FILE 'BIOSIS' ENTERED AT 14:08:59 ON 14 JUL 2005  
Copyright (c) 2005 The Thomson Corporation

FILE COVERS 1969 TO DATE.  
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT  
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 8 July 2005 (20050708/ED)

FILE RELOADED: 19 October 2003.

=> fil pascal

FILE 'PASCAL' ENTERED AT 14:09:02 ON 14 JUL 2005

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FILE LAST UPDATED: 11 JUL 2005 <20050711/UP>

FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE  
IN THE BASIC INDEX (/BI) FIELD <<<

=> fil jicst

FILE 'JICST-EPLUS' ENTERED AT 14:09:05 ON 14 JUL 2005

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FILE COVERS 1985 TO 11 JUL 2005 (20050711/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED  
TERM (/CT) THESAURUS RELOAD.

=> fil embase

FILE 'EMBASE' ENTERED AT 14:09:08 ON 14 JUL 2005

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FILE COVERS 1974 TO 7 Jul 2005 (20050707/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate  
substance identification.

=> fil cancerlit

FILE 'CANCERLIT' ENTERED AT 14:09:12 ON 14 JUL 2005

FILE COVERS 1963 TO 15 Nov 2002 (20021115/ED)

On July 28, 2002, CANCERLIT was reloaded. See HELP RLOAD for details.

CANCERLIT thesauri in the /CN, /CT, and /MN fields incorporate the  
MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

This file contains CAS Registry Numbers for easy and accurate substance  
identification.

=> fil drugu

FILE 'DRUGU' ENTERED AT 14:09:15 ON 14 JUL 2005

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FILE LAST UPDATED: 13 JUL 2005 <20050713/UP>

>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> FILE COVERS 1983 TO DATE <<<  
>>> THESAURUS AVAILABLE IN /CT <<<

=> fil scisearch  
FILE 'SCISEARCH' ENTERED AT 14:09:19 ON 14 JUL 2005  
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FILE COVERS 1974 TO 8 Jul 2005 (20050708/ED)

=> fil wpix  
FILE 'WPIX' ENTERED AT 14:09:23 ON 14 JUL 2005  
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FILE LAST UPDATED: 12 JUL 2005 <20050712/UP>  
MOST RECENT DERWENT UPDATE: 200544 <200544/DW>  
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,  
PLEASE VISIT:  
[http://www.stn-international.de/training\\_center/patents/stn\\_guide.pdf](http://www.stn-international.de/training_center/patents/stn_guide.pdf) <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE  
<http://thomsonderwent.com/coverage/latestupdates/> <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER  
GUIDES, PLEASE VISIT:  
<http://thomsonderwent.com/support/userguides/> <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT  
DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX  
FIRST VIEW - FILE WPIFV.  
FOR FURTHER DETAILS: <http://www.thomsonderwent.com/dwpifv> <<<

>>> THE CPI AND EPI MANUAL CODES HAVE BEEN REVISED FROM UPDATE 200501.  
PLEASE CHECK:  
<http://thomsonderwent.com/support/dwpioref/reftools/classification/code-revision/>  
FOR DETAILS. <<<

=> fil conf  
FILE 'CONF' ENTERED AT 14:09:27 ON 14 JUL 2005  
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FILE LAST UPDATED: 8 JUL 2005 <20050708/UP>  
FILE COVERS 1976 TO DATE.

=> fil confsci  
FILE 'CONFSCI' ENTERED AT 14:09:32 ON 14 JUL 2005  
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FILE COVERS 1973 TO 25 May 2005 (20050525/ED)

=> fil uspatfull  
FILE 'USPATFULL' ENTERED AT 14:09:35 ON 14 JUL 2005  
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 12 Jul 2005 (20050712/PD)  
FILE LAST UPDATED: 12 Jul 2005 (20050712/ED)  
HIGHEST GRANTED PATENT NUMBER: US6918136

HIGHEST APPLICATION PUBLICATION NUMBER: US2005150027  
CA INDEXING IS CURRENT THROUGH 12 Jul 2005 (20050712/UPCA)  
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 12 Jul 2005 (20050712/PD)  
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2005  
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2005

```
>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<
```

```
>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<
```

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=> fil uspat2

FILE 'USPAT2' ENTERED AT 14:09:39 ON 14 JUL 2005  
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FILE COVERS 2001 TO PUBLICATION DATE: 14 Jul 2005 (20050714/PD)  
FILE LAST UPDATED: 14 Jul 2005 (20050714/ED)  
HIGHEST GRANTED PATENT NUMBER: US2004225788  
HIGHEST APPLICATION PUBLICATION NUMBER: US2005155125  
CA INDEXING IS CURRENT THROUGH 14 Jul 2005 (20050714/UPCA)  
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 14 Jul 2005 (20050714/PD)  
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2005  
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2005

USPAT2 is a companion file to USPATFULL. USPAT2 contains full text of the latest US publications, starting in 2001, for the inventions covered in USPATFULL. USPATFULL contains full text of the original published US patents from 1971 to date and the original applications from 2001. In addition, a USPATFULL record for an invention contains a complete list of publications that may be searched in standard search fields, e.g., /PN, /PK, etc.

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Use USPATALL when searching terms such as patent assignees, classifications, or claims, that may potentially change from the earliest to the latest publication.

=>

=> fil toxcenter

FILE 'TOXCENTER' ENTERED AT 15:02:04 ON 14 JUL 2005

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FILE COVERS 1907 TO 12 Jul 2005 (20050712/ED)

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TOXCENTER has been enhanced with new files segments and search fields.  
See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary. See <http://www.nlm.nih.gov/mesh/> and [http://www.nlm.nih.gov/pubs/techbull/nd04/nd04\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html) for a description of changes.

=>

=> file stnguide

FILE 'STNGUIDE' ENTERED AT 14:09:51 ON 14 JUL 2005

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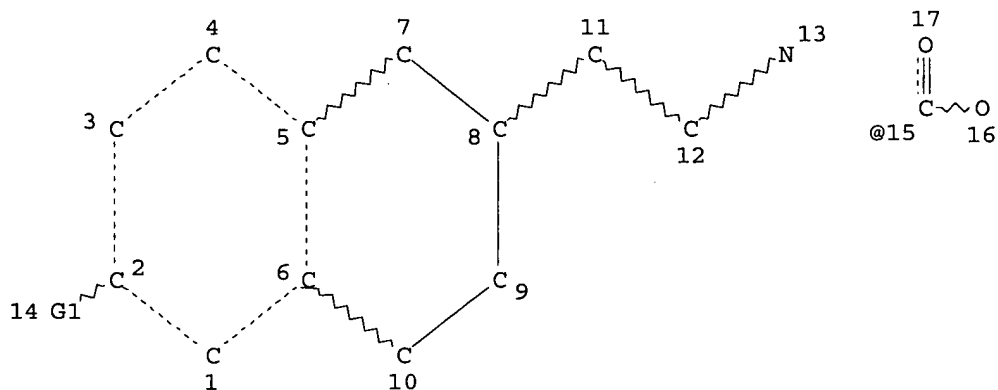
FILE CONTAINS CURRENT INFORMATION.

LAST RELOADED: Jul 8, 2005 (20050708/UP).

=&gt;

=&gt; d que stat l15

L6 STR



VAR G1=X/15

NODE ATTRIBUTES:

CONNECT IS E4 RC AT 8

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

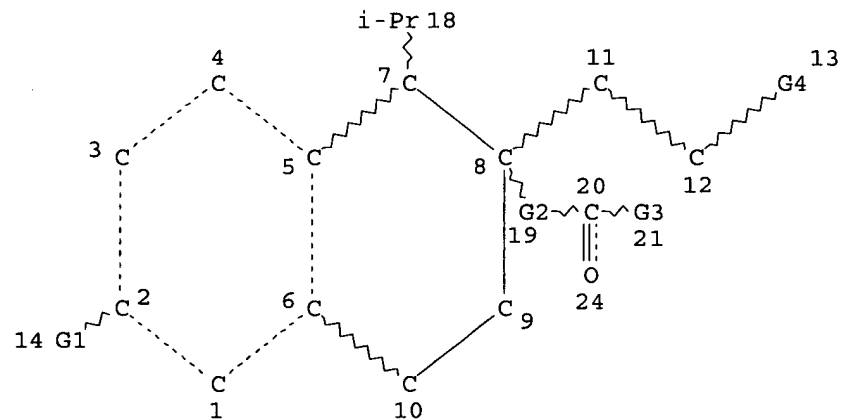
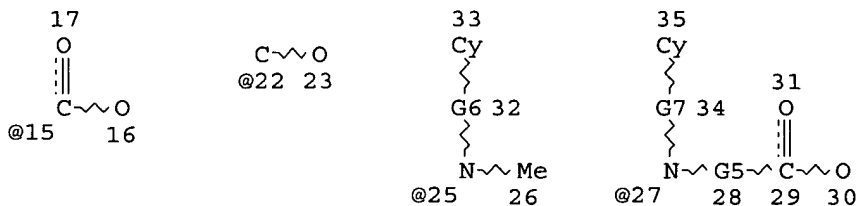
RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 17

STEREO ATTRIBUTES: NONE

L8 312 SEA FILE=REGISTRY SSS FUL L6

L13 STR



```

VAR G1=X/15
REP G2=(0-8) A
VAR G3=O/22
VAR G4=25/27
REP G5=(1-6) C
REP G6=(1-10) A
REP G7=(1-10) A
NODE ATTRIBUTES:
CONNECT IS E4 RC AT 8
DEFAULT MLEVEL IS ATOM
GGCAT IS UNS AT 33
GGCAT IS UNS AT 35
DEFAULT ECLEVEL IS LIMITED

```

```

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 35

```

```

STEREO ATTRIBUTES: NONE
L15      135 SEA FILE=REGISTRY SUB=L8 SSS FUL L13

```

```

100.0% PROCESSED      279 ITERATIONS      135 ANSWERS
SEARCH TIME: 00.00.01

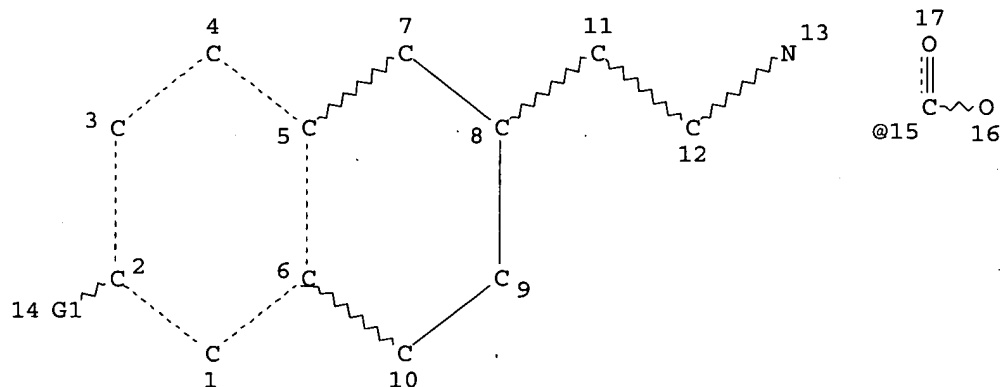
```

=> d que 141

```

L1      1 SEA FILE=HCAPLUS ABB=ON PLU=ON US2003-643699/APPS
L3      TRANSFER PLU=ON L1 1- RN :      3 TERMS
L4      3 SEA FILE=REGISTRY ABB=ON PLU=ON L3
L6      STR

```



```

VAR G1=X/15
NODE ATTRIBUTES:
CONNECT IS E4 RC AT 8
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

```

```

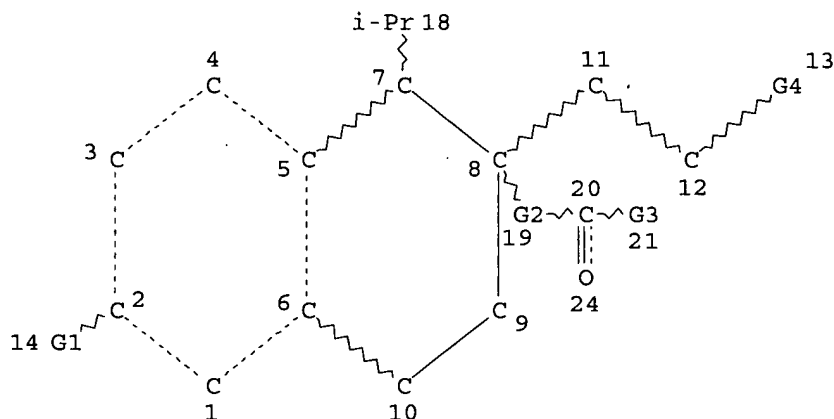
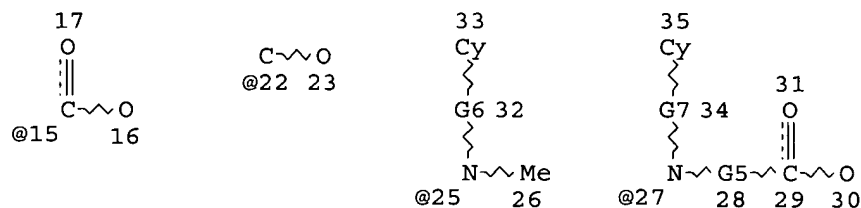
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 17

```

```

STEREO ATTRIBUTES: NONE
L8      312 SEA FILE=REGISTRY SSS FUL L6
L13     STR

```



VAR G1=X/15  
 REP G2=(0-8) A  
 VAR G3=O/22  
 VAR G4=25/27  
 REP G5=(1-6) C  
 REP G6=(1-10) A  
 REP G7=(1-10) A  
 NODE ATTRIBUTES:  
 CONNECT IS E4 RC AT 8  
 DEFAULT MLEVEL IS ATOM  
 GGCAT IS UNS AT 33  
 GGCAT IS UNS AT 35  
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
 RING(S) ARE ISOLATED OR EMBEDDED  
 NUMBER OF NODES IS 35

STEREO ATTRIBUTES: NONE

L15 135 SEA FILE=REGISTRY SUB=L8 SSS FUL L13  
 L16 1 SEA FILE=REGISTRY ABB=ON PLU=ON L15 AND L4  
 L23 QUE ABB=ON PLU=ON (CA OR ?CALCIUM?) (2A) (?CHANNEL? OR ?  
 SIGNAL?)  
 L25 136 SEA FILE=HCAPLUS ABB=ON PLU=ON L15 (L) L23  
 L27 134 SEA FILE=REGISTRY ABB=ON PLU=ON L15 NOT L16  
 L28 69 SEA FILE=HCAPLUS ABB=ON PLU=ON L27  
 L29 7 SEA FILE=HCAPLUS ABB=ON PLU=ON 116644-53-2D?  
 L30 76 SEA FILE=HCAPLUS ABB=ON PLU=ON L28 OR L29  
 L31 21 SEA FILE=HCAPLUS ABB=ON PLU=ON L30 (L) L23  
 L35 QUE ABB=ON PLU=ON ?HYPERTENS? OR ?ANGINA? OR ?ISCHEM?  
 OR ?ARRHYTHM? OR ?CARDIAC? OR ?CARDIO? OR HEART  
 L38 152 SEA FILE=HCAPLUS ABB=ON PLU=ON L15 (L) L35  
 L39 47 SEA FILE=HCAPLUS ABB=ON PLU=ON L25 AND L38



L40 59 SEA FILE=HCAPLUS ABB=ON PLU=ON L31 OR L39  
 L41 53 SEA FILE=HCAPLUS ABB=ON PLU=ON L40 AND (AY<2002 OR PY<2002  
 OR PRY<2002)

=> d his 145

(FILE 'USPATFULL, USPAT2' ENTERED AT 12:49:22 ON 14 JUL 2005)  
 L45 33 S L44 AND (AY<2002 OR PY<2002 OR PRY<2002)

=> d que nos 145

L6 STR  
 L8 312 SEA FILE=REGISTRY SSS FUL L6  
 L13 STR  
 L15 135 SEA FILE=REGISTRY SUB=L8 SSS FUL L13  
 L23 QUE ABB=ON PLU=ON (CA OR ?CALCIUM?) (2A) (?CHANNEL? OR ?  
 SIGNAL?)  
 L35 QUE ABB=ON PLU=ON ?HYPERTENS? OR ?ANGINA? OR ?ISCHEM?  
 OR ?ARRHYTHM? OR ?CARDIAC? OR ?CARDIO? OR HEART  
 L42 58 SEA L15  
 L44 38 SEA L42 AND (L23/IT,ST,CC OR L35/IT,ST,CC)  
 L45 33 SEA L44 AND (AY<2002 OR PY<2002 OR PRY<2002)

=> d que nos 190

L84 43 SEA FILE=WPIX ABB=ON PLU=ON (MIBEFRADIL/BIX OR POSICOR/BIX  
 OR RO-40-5967/BIX)  
 L85 16553 SEA FILE=WPIX ABB=ON PLU=ON A61P009?/IPC  
 L86 44034 SEA FILE=WPIX ABB=ON PLU=ON (B14-F01? OR C14-F01? OR  
 B14-F02? OR C14-F02?)/MC  
 L87 30 SEA FILE=WPIX ABB=ON PLU=ON L84 AND (L85 OR L86)  
 L88 18 SEA FILE=WPIX ABB=ON PLU=ON L87 AND ((CA/BIX OR ?CALCIUM?/BIX  
 ) (2A) (?CHANNEL?/BIX OR ?SIGNAL?/BIX))  
 L89 17 SEA FILE=WPIX ABB=ON PLU=ON L87 AND (AY<2002 OR PY<2002 OR  
 PRY<2002)  
 L90 9 SEA FILE=WPIX ABB=ON PLU=ON L88 AND L89

=> d que nos 182

L6 STR  
 L8 312 SEA FILE=REGISTRY SSS FUL L6  
 L13 STR  
 L15 135 SEA FILE=REGISTRY SUB=L8 SSS FUL L13  
 L23 QUE ABB=ON PLU=ON (CA OR ?CALCIUM?) (2A) (?CHANNEL? OR ?  
 SIGNAL?)  
 L68 SEL ABB=ON PLU=ON L15 1- CHEM : 154 TERMS  
 L69 935 SEA FILE=EMBASE ABB=ON PLU=ON L68  
 L70 511 SEA FILE=EMBASE ABB=ON PLU=ON L69 AND L23  
 L77 47 SEA FILE=EMBASE ABB=ON PLU=ON L70 AND ((CA/CT OR ?CALCIUM?/CT  
 ) (2A) (?CHANNEL?/CT OR ?SIGNAL?/CT))  
 L79 39 SEA FILE=EMBASE ABB=ON PLU=ON L77/MAJ  
 L80 24 SEA FILE=EMBASE ABB=ON PLU=ON L79 AND (PY<2002 OR MY<2002)  
 L82 6 SEA FILE=EMBASE ABB=ON PLU=ON L80 AND (?HYPERTENS?/CT OR  
 ?ANGINA?/CT OR ?ISCHEM?/CT OR ?ARRHYTHM?/CT OR ?CARDIAC?/CT OR  
 ?CARDIO?/CT OR HEART/CT)

=> d que nos 152

L1 1 SEA FILE=HCAPLUS ABB=ON PLU=ON US2003-643699/APPS  
 L3 TRANSFER PLU=ON L1 1- RN : 3 TERMS

L4 3 SEA FILE=REGISTRY ABB=ON PLU=ON L3  
L6 STR  
L8 312 SEA FILE=REGISTRY SSS FUL L6  
L13 STR  
L15 135 SEA FILE=REGISTRY SUB=L8 SSS FUL L13  
L16 1 SEA FILE=REGISTRY ABB=ON PLU=ON L15 AND L4  
L23 QUE ABB=ON PLU=ON (CA OR ?CALCIUM?) (2A) (?CHANNEL? OR ?  
SIGNAL?)  
L27 134 SEA FILE=REGISTRY ABB=ON PLU=ON L15 NOT L16  
L35 QUE ABB=ON PLU=ON ?HYPERTENS? OR ?ANGINA? OR ?ISCHEM?  
OR ?ARRHYTHM? OR ?CARDIAC? OR ?CARDIO? OR HEART  
L46 326 SEA FILE=TOXCENTER ABB=ON PLU=ON L15  
L47 229 SEA FILE=TOXCENTER ABB=ON PLU=ON L46 AND L23  
L48 164 SEA FILE=TOXCENTER ABB=ON PLU=ON L47 AND L35  
L49 12 SEA FILE=TOXCENTER ABB=ON PLU=ON L48 AND REVIEW/DT  
L50 36 SEA FILE=TOXCENTER ABB=ON PLU=ON L27  
L51 35 SEA FILE=TOXCENTER ABB=ON PLU=ON L50 AND (PY<2002 OR  
MY<2002)  
L52 47 SEA FILE=TOXCENTER ABB=ON PLU=ON L49 OR L51

=> d his 167

(FILE 'MEDLINE, BIOSIS, PASCAL, JICST-EPLUS, CANCERLIT, DRUGU, SCISEARCH'  
ENTERED AT 13:01:21 ON 14 JUL 2005)

L67 83 S L65 AND (?HYPERTENS? OR ?ANGINA? OR ?ISCHEM? OR ?ARRHYTH? OR

=> d que nos 167

L6 STR  
L8 312 SEA FILE=REGISTRY SSS FUL L6  
L13 STR  
L15 135 SEA FILE=REGISTRY SUB=L8 SSS FUL L13  
L23 QUE ABB=ON PLU=ON (CA OR ?CALCIUM?) (2A) (?CHANNEL? OR ?  
SIGNAL?)  
L35 QUE ABB=ON PLU=ON ?HYPERTENS? OR ?ANGINA? OR ?ISCHEM?  
OR ?ARRHYTHM? OR ?CARDIAC? OR ?CARDIO? OR HEART  
L54 SEL PLU=ON L15 1- CHEM : 154 TERMS  
L55 2569 SEA L54  
L57 925 SEA L55 (10A) L23  
L59 981 SEA L55 (10A) L35  
L60 483 SEA L57 AND L59  
L61 269 DUP REM L60 (214 'DUPLICATES REMOVED')  
L62 229 SEA L61 AND L23/IT,ST,CT,CC,TI  
L63 246 SEA L61 AND L35/IT,ST,CT,CC,TI  
L64 211 SEA L62 AND L63  
L65 142 SEA L64 AND (AY<2002 OR PY<2002 OR PRY<2002 OR MY<2002)  
L67 83 SEA L65 AND (?HYPERTENS? OR ?ANGINA? OR ?ISCHEM? OR ?ARRHYTH?  
OR ?ANTIHYPERTENS? OR ?ANTIANGINA? OR ?ANTIISCHEM? OR ?ANTIARRH  
YTHM?)/IT,ST,CC,CT,TI

=> dup rem 141 145 190 182 152 167

FILE 'HCAPLUS' ENTERED AT 14:13:01 ON 14 JUL 2005

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PROCESSING COMPLETED FOR L41

PROCESSING COMPLETED FOR L45

PROCESSING COMPLETED FOR L90

PROCESSING COMPLETED FOR L82

PROCESSING COMPLETED FOR L52

PROCESSING COMPLETED FOR L67

L103 198 DUP REM L41 L45 L90 L82 L52 L67 (33 DUPLICATES REMOVED)

ANSWERS '1-53' FROM FILE HCAPLUS

ANSWERS '54-79' FROM FILE USPATFULL

ANSWERS '80-85' FROM FILE WPIX

ANSWERS '86-90' FROM FILE EMBASE

ANSWERS '91-131' FROM FILE TOXCENTER

ANSWERS '132-140' FROM FILE MEDLINE

ANSWERS '141-172' FROM FILE BIOSIS

ANSWERS '173-177' FROM FILE PASCAL

ANSWERS '178-195' FROM FILE DRUGU

ANSWERS '196-198' FROM FILE SCISEARCH

=> file stnguide

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FILE CONTAINS CURRENT INFORMATION.  
LAST RELOADED: Jul 8, 2005 (20050708/UP).

=> d ibib ed ab hitind hitstr

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L103 ANSWER 1 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2003:301058 HCAPLUS

DOCUMENT NUMBER: 138:297661

TITLE: Mibefradil-based compounds as calcium channel blockers useful in the treatment of hypertension and angina

INVENTOR(S): Druzgala, Pascal; Milner, Peter G.; Pfister, Jurg R.; Zhang, Xiaoming

PATENT ASSIGNEE(S): Aryx Therapeutics, USA

SOURCE: PCT Int. Appl., 50 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003031415	A1	20030417	WO 2002-US32562	20021010 <--
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
CA 2462913	AA	20030417	CA 2002-2462913	20021010 <--
US 2003130330	A1	20030710	US 2002-269139	20021010 <--
US 6608097	B2	20030819		
EP 1438297	A1	20040721	EP 2002-773743	20021010 <--
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK			
JP 2005508949	T2	20050407	JP 2003-534399	20021010 <--
US 2004034237	A1	20040219	US 2003-643699	20030818 <--
PRIORITY APPLN. INFO.:			US 2001-328588P	P 20011010 <--
			US 2002-269139	A1 20021010
			WO 2002-US32562	W 20021010

OTHER SOURCE(S): MARPAT 138:297661

ED Entered STN: 18 Apr 2003

AB The invention provides mibefradil-based calcium channel blockers I [X = bond, (CH<sub>2</sub>)<sub>n</sub>, O, S, O(CH<sub>2</sub>)<sub>n</sub> (n = 1-6); R<sub>1</sub> = C1-6 alkyl, optionally substituted with OH or NH<sub>2</sub>; R<sub>2</sub> = F, COOR<sub>5</sub> (R<sub>5</sub> = R<sub>1</sub>); R<sub>3</sub> = CH<sub>3</sub>, (CH<sub>2</sub>)<sub>n</sub>COOR<sub>6</sub>, (n = 1-6; R<sub>6</sub> = R<sub>1</sub>); R<sub>4</sub> = (CH<sub>2</sub>)<sub>n</sub>COR<sub>7</sub>R<sub>8</sub>, (CH<sub>2</sub>)<sub>n</sub>R<sub>10</sub>R<sub>11</sub>, Q<sub>1</sub>; R<sub>7</sub> = O, NH, NR<sub>9</sub>, R<sub>8</sub> = optionally substituted aryl or heterocyclyl; R<sub>9</sub> = C1-6 alkyl; R<sub>10</sub> = O, S, SO, SO<sub>2</sub>, NH, NR<sub>12</sub>, N(CH<sub>2</sub>)<sub>m</sub>COOR<sub>13</sub>; R<sub>11</sub> = aryl or heterocyclyl optionally substituted with (CH<sub>2</sub>)<sub>n</sub>COOR<sub>14</sub>, R<sub>12</sub>-R<sub>14</sub> = R<sub>1</sub>; R<sub>15</sub> = (CH<sub>2</sub>)<sub>n</sub> COOR<sub>16</sub>, R<sub>16</sub> = R<sub>1</sub>; R<sub>17</sub> = absent or COOR<sub>18</sub>; R<sub>18</sub> = R<sub>1</sub>; n = 1-6] useful in the treatment of hypertension, angina pectoris, ischemia, arrhythmias and cardiac insufficiency.

IC ICM C07D235-08

ICS C07C211-43; C07C233-08; C07C317-14; A61K031-415

CC 1-8 (Pharmacology)

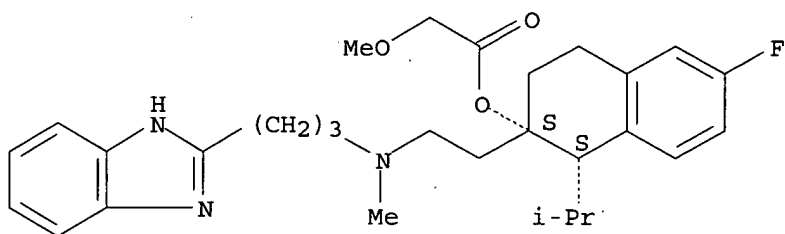
IT 116644-53-2D, Mibefradil, derivs.  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)

IT 116644-53-2D, Mibefradil, derivs.  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib ed ab hitind hitstr 2-53

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, TOXCENTER, MEDLINE, BIOSIS, PASCAL, DRUGU, SCISEARCH, EMBASE, WPIX' - CONTINUE? (Y)/N:y

L103 ANSWER 2 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 2  
 ACCESSION NUMBER: 2003:678514 HCAPLUS  
 DOCUMENT NUMBER: 139:191440  
 TITLE: Methods of treating or preventing a cardiovascular condition using a cyclooxygenase-1 inhibitor  
 INVENTOR(S): Krul, Elaine S.  
 PATENT ASSIGNEE(S): USA  
 SOURCE: U.S. Pat. Appl. Publ., 32 pp.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003162824	A1	20030828	US 2002-292255	20021112 <--
PRIORITY APPLN. INFO.:			US 2001-331346P	P 20011112 <--
			US 2001-338291P	P 20011113 <--

OTHER SOURCE(S): MARPAT 139:191440

ED Entered STN: 29 Aug 2003

AB Methods for treating or preventing one or more cardiovascular conditions in a subject comprises treating the subject with a therapeutically

effective amount of a selective cyclooxygenase-1 inhibitor or a pharmaceutically-acceptable salt, tautomer or prodrug thereof alone or in combination with either a drug used in the treatment or prevention of a cardiovascular condition or a non-drug therapy used in the treatment of a cardiovascular condition. Cyclooxygenase-1 inhibitor, 5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-(trifluoromethyl)pyrazole (I), was prepared from 4'-chloroacetophenone and (4-methoxyphenyl)hydrazine hydrochloride. I inhibited development of atherosclerosis in cholesterol-fed apoE knockout mice.

IC ICM A61K031-415

INCL 514406000

CC 1-8 (Pharmacology)

IT 52-53-9, Verapamil 390-64-7, Prenylamine 3416-26-0, Lidoflazine 6621-47-2, Perhexiline 15793-40-5, Terodiline 16662-47-8, Gallopamil 21829-25-4, Nifedipine 31309-39-4, Medipine 39562-70-4, Nitrendipine 42399-41-7, Diltiazem 55985-32-5, Nicardipine 63675-72-9, Nisoldipine 64706-54-3, Bepridil 72509-76-3, Felodipine 75530-68-6, Nilvadipine 75695-93-1, Isradipine 86780-90-7, Aranidipine 88150-42-9, Amlodipine 96125-53-0, Clentiazem 100427-26-7, Lercanidipine 103890-78-4, Lacidipine 104713-75-9, Barnidipine 105979-17-7, Benidipine 111011-63-3, Efonidipine 116476-13-2, Semotiadil **116644-53-2**, Mibefradil 119413-55-7, Elgodipine 132203-70-4, Cilnidipine  
 RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (calcium channel blocker; cyclooxygenase-1 inhibitor for treating or preventing cardiovascular conditions)

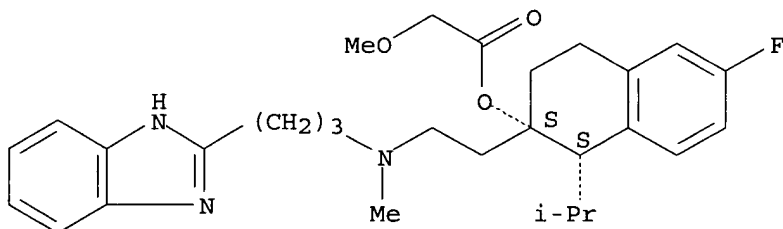
IT **116644-53-2**, Mibefradil

RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (calcium channel blocker; cyclooxygenase-1 inhibitor for treating or preventing cardiovascular conditions)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 3 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 2003:300530 HCAPLUS

DOCUMENT NUMBER: 138:314620

TITLE: Calcium channel multibinding drugs, and uses

INVENTOR(S): Ji, Yu-Hua; Natarajan, Maya; Griffin, John H.; Jenkins, Thomas E.

PATENT ASSIGNEE(S): Theravance, Inc., USA

SOURCE: U.S. Pat. Appl. Publ., 183 pp., Cont.-in-part of U.S. Ser. No. 325,557, abandoned.

DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 31  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003073127	A1	20030417	US 1999-456429	19991208 <--
US 6897305	B2	20050524		
CA 2318806	AA	19991216	CA 1999-2318806	19990607 <--
CA 2319142	AA	19991216	CA 1999-2319142	19990607 <--
CA 2319153	AA	19991216	CA 1999-2319153	19990607 <--
WO 9963984	A1	19991216	WO 1999-US11801	19990607 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
WO 9963932	A2	19991216	WO 1999-US12724	19990607 <--
WO 9963932	A3	20000203		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
WO 9964045	A1	19991216	WO 1999-US12754	19990607 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9945511	A1	19991230	AU 1999-45511	19990607 <--
AU 9946726	A	19991230	AU 1999-46726	19990607 <--
AU 9946726	A1	19991230		
EP 1085879	A2	20010328	EP 1999-928442	19990607 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
EP 1085890	A1	20010328	EP 1999-930122	19990607 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
EP 1089749	A1	20010411	EP 1999-928447	19990607 <--
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JP 2002517437	T2	20020618	JP 2000-553053	19990607 <--
ZA 2000004562	A	20011130	ZA 2000-4562	20000831 <--
ZA 2000004563	A	20011130	ZA 2000-4563	20000831 <--
ZA 2000004564	A	20011130	ZA 2000-4564	20000831 <--

US 2003044845	A1	20030306	US 2002-75017	20020213	<--
US 2004242561	A1	20041202	US 2004-877368	20040625	<--
PRIORITY APPLN. INFO.:			US 1998-88465P	P	19980608 <--
			US 1998-93068P	P	19980716 <--
			US 1998-103866P	P	19981012 <--
			US 1999-325557	B2	19990604 <--
			US 1999-327096	B1	19990607 <--
			WO 1999-US11801	W	19990607 <--
			WO 1999-US12724	W	19990607 <--
			WO 1999-US12754	W	19990607 <--
			US 1999-456429	A1	19991208 <--
			US 2000-499176	B1	20000207 <--

OTHER SOURCE(S): MARPAT 138:314620

ED Entered STN: 18 Apr 2003

AB Multibinding compds. are disclosed. The compds. of the invention comprise 2-10 ligands covalently connected via linker groups, each of the ligands being capable of binding to a ligand-binding site in a calcium channel, thereby modulating the biol. activities thereof. The compds. of the invention may be used to treat diseases or conditions resulting from calcium channel activity. Pharmaceutical compns. are also disclosed.

IC ICM G01N033-53

ICS G01N033-567; C07D279-16; C07D231-56

INCL 435007100; 435007200; 544051000; 548361100

CC 1-12 (Pharmacology)

Section cross-reference(s): 63

IT 52-53-9D, Verapamil, ligand-linker conjugates 152-11-4D, Verelan, ligand-linker conjugates 15793-40-5D, Terodiline, ligand-linker conjugates 21306-56-9D, QX-314, ligand-linker conjugates 21829-25-4D, Nifedipine, ligand-linker conjugates 39562-70-4D, Nitrendipine, ligand-linker conjugates 42399-41-7D, Diltiazem, ligand-linker conjugates 55837-25-7D, Buflomedil, ligand-linker conjugates 55985-32-5D, Nicardipine, ligand-linker conjugates 57010-18-1D, Ro-11-2933, ligand-linker conjugates 64706-54-3D, Bepridil, ligand-linker conjugates 66085-59-4D, Nimodipine, ligand-linker conjugates 72509-76-3D, Felodipine, ligand-linker conjugates 72527-29-8D, GS-386, ligand-linker conjugates 72803-02-2D, Darodipine, ligand-linker conjugates 75530-68-6D, Nilvadipine, ligand-linker conjugates 75695-93-1D, Isradipine, ligand-linker conjugates 77191-36-7D, Nefiracetam, ligand-linker conjugates 78370-13-5D, Emopamil, ligand-linker conjugates 79700-61-1D, Dopropidil, ligand-linker conjugates 83200-10-6D, Anipamil, ligand-linker conjugates 85175-67-3D, Zatebradine, ligand-linker conjugates 86780-90-7D, Aranidipine, ligand-linker conjugates 88150-42-9D, Amlodipine, ligand-linker conjugates 88594-08-5D, CD-349, ligand-linker conjugates 89194-77-4D, Bisaramil, ligand-linker conjugates 89226-50-6D, Manidipine, ligand-linker conjugates 90729-41-2D, Oxodipine, ligand-linker conjugates 90779-69-4D, Atosiban, ligand-linker conjugates 93035-32-6D, Tamolarizine, ligand-linker conjugates 94739-29-4D, Lemildipine, ligand-linker conjugates 95635-55-5D, Ranolazine, ligand-linker conjugates 96125-53-0D, Clentiazem, ligand-linker conjugates 96515-73-0D, Palonidipine, ligand-linker conjugates 97290-20-5D, UK 55444, ligand-linker conjugates 97938-30-2D, Vexibinol, ligand-linker conjugates 99522-79-9D, Pranidipine, ligand-linker conjugates 100427-26-7D, Lercanidipine, ligand-linker conjugates 101041-95-6D, Org-30029, ligand-linker conjugates 101477-55-8D, Lomerizine, ligand-linker conjugates 102097-78-9D, DHP-218, ligand-linker conjugates 103129-81-3D, R-(+)-Amlodipine, ligand-linker conjugates 103129-82-4D, S-(-)-Amlodipine, ligand-linker conjugates 103377-41-9D, Monatepil, ligand-linker conjugates 103486-79-9D, Belfosdil, ligand-linker conjugates 103745-39-7D, Fasudil, ligand-linker



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ligand-linker conjugates 116476-13-2D, Semotiadil, ligand-linker  
conjugates 116476-17-6D, SD-3212, ligand-linker conjugates  
**116644-53-2D**, Mibefradil, ligand-linker conjugates 117023-62-8D,  
AHR 16303B, ligand-linker conjugates 118587-22-7D, BBR-2160,  
ligand-linker conjugates 119413-55-7D, Elgodipine, ligand-linker  
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ligand-linker conjugates 120934-96-5D, FPL-64176, ligand-linker  
conjugates 121346-32-5D, SR-33805, ligand-linker conjugates  
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SKF-96365, ligand-linker conjugates 132194-66-2D, S-12968, ligand-linker  
conjugates 132203-70-4D, Cilnidipine, ligand-linker conjugates  
133714-64-4D, UK-84149, ligand-linker conjugates 133743-71-2D, AE-0047,  
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134142-91-9D, AHR-16462B, ligand-linker conjugates 135462-05-4D, XT-044,  
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NNC-09-0026, ligand-linker conjugates 141430-36-6D, SB-201823,  
ligand-linker conjugates 141626-36-0D, Dronedarone, ligand-linker  
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RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(calcium channel multibinding drugs, and uses)

IT 116644-53-2D, Mibefradil, ligand-linker conjugates

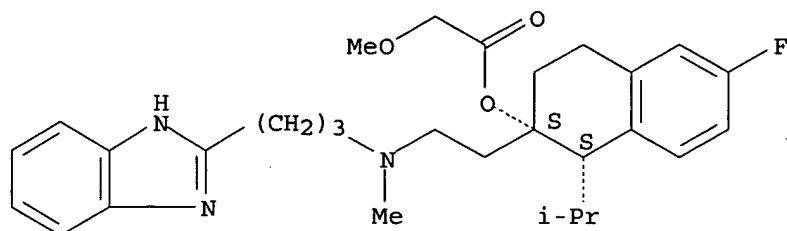
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(calcium channel multibinding drugs, and uses)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 4 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 9

ACCESSION NUMBER: 2000:881886 HCAPLUS

DOCUMENT NUMBER: 134:110304

TITLE: Quantitative analysis of vascular to cardiac selectivity of L- and T-type voltage-operated calcium channel antagonists in human tissues

AUTHOR(S): Angus, J. A.; Sarsero, D.; Fujiwara, T.; Molenaar, P.; Xi, Q.

CORPORATE SOURCE: Department of Pharmacology, The University of Melbourne, Parkville, 3010, Australia

SOURCE: Clinical and Experimental Pharmacology and Physiology (2000), 27(12), 1019-1021

CODEN: CEXPB9; ISSN: 0305-1870

PUBLISHER: Blackwell Science Asia Pty Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 17 Dec 2000

AB Classical L-type voltage-operated calcium channel (VOCC) antagonists dilate blood vessels, depress myocardial contractility and slow cardiac conduction. We compared four L-type VOCC antagonists and a novel tetralol derivative, mibefradil, reportedly 10-fold more selective for T- (transient) over L-type VOCC in two in vitro assays of human tissue, namely isolated small arteries from the aortic vasa vasorum in a myograph and right atrial trabeculae muscle under isometric force conditions. In arteries contracted with K<sup>+</sup> (62 mmol/L), the relaxation pIC<sub>50</sub> values for the VOCC antagonists felodipine, nifedipine, amlodipine, verapamil and mibefradil were 8.30, 7.78, 6.64, 6.26 and 6.22, resp. In atrial trabeculae, the pIC<sub>50</sub> values to inhibit the inotropic response to a submaximal concentration of isoprenaline (6 nmol/L) for felodipine, nifedipine, verapamil, amlodipine and mibefradil were 7.21, 6.95, 6.91, 5.94 and 4.61, resp. Taking the anti-log (pIC<sub>50</sub> vessel - pIC<sub>50</sub> atrium) the vascular relaxation to cardiac depression potency ratios for mibefradil, felodipine, nifedipine, amlodipine and verapamil were 41, 12, 7, 5 and 0.22, resp. We conclude that, in human tissue assays, perhaps T- over L-type VOCC selectivity confers the most favorable vascular selectivity on mibefradil. Alternatively, splice variants of L-type VOCC in the vasculature (Ca<sub>v</sub>1.2b) may be more sensitive to mibefradil than the splice variants in the heart (Ca<sub>v</sub>1.2a).

CC 1-8 (Pharmacology)

Section cross-reference(s): 13

IT 52-53-9, Verapamil 21829-25-4, Nifedipine 72509-76-3, Felodipine

88150-42-9, Amlodipine 116644-53-2, Mibefradil

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(quant. anal. of vascular to cardiac selectivity of L- and T-type voltage-operated calcium channel antagonists in human tissues)

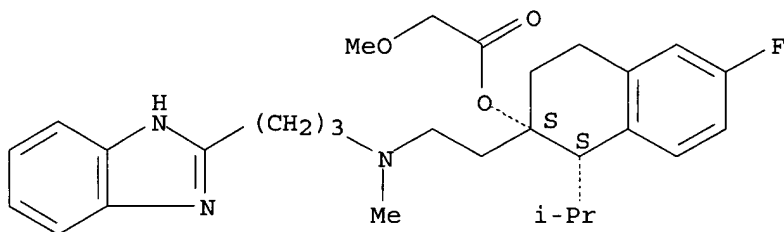
IT 116644-53-2, Mibefradil

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (quant. anal. of vascular to **cardiac** selectivity of L- and  
 T-type voltage-operated **calcium channel** antagonists  
 in human tissues)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 5 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 10

ACCESSION NUMBER: 2000:29219 HCAPLUS

DOCUMENT NUMBER: 132:58970

TITLE: Combination of calcium channel blockers and  $\beta$ -blockers for patients with exercise-induced angina pectoris: beneficial effect of calcium channel blockers largely determined by their effect on heart rate

AUTHOR(S): Cleophas, Ton J.; Van der Sluijs, Johan; Van der Vring, Jan A.; Daniels, Marcel C.; Holwerda, Klaas J.; Withagen, Adrie J.; Schelling, Adri; Hendriks, Maarten G.; Zwinderman, Aeilko H.

CORPORATE SOURCE: Netherlands Working Group on Cardiovascular Research (WCN), European Interuniversity College of Pharmaceutical Medicine, Merwede Hospital, Dardrecht, 3300 AH, Neth.

SOURCE: Journal of Clinical Pharmacology (1999), 39(7), 738-746

CODEN: JCPCBR; ISSN: 0091-2700

PUBLISHER: Sage Publications

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 13 Jan 2000

AB The combination of calcium channel blockers and  $\beta$ -blockers is more effective for the treatment of exercise-induced angina pectoris than is  $\beta$ -blocker monotherapy. As ischemia in exercise-induced angina is essentially preceded by an increase in heart rate, calcium channel blockers with a neg. chronotropic property may perform better for this purpose than nonchronotropic compds. A 335-patient, 10-wk, double-blind, parallel-group comparison of 5 and 10 mg amlodipine, 200 and 300 mg diltiazem, and 50 and 100 mg mibefradil treatment added to basal  $\beta$ -blocker treatment was performed. Exercise testing (ETT) was performed by bicycle ergometry. All of the calcium channels blockers delayed the onset of 1-mm ST-segment depression on ETT. Mibefradil, in both low- and high-dose treatments, produced the largest delays. A stepwise logistic regression anal. revealed that this beneficial effect of

calcium channel blockers was largely dependent on their effect on heart rate. Serious symptoms of dizziness likewise occurred more frequently on mibefradil and caused several patients on mibefradil to withdraw from the trial. Calcium channel blockers with a neg. chronotropic property provide a good delay of ischemia in patients with exercise-induced angina, but the concomitant risk of intolerable dizziness may reduce this benefit.

CC 1-8 (Pharmacology)

IT 42399-41-7, Diltiazem 88150-42-9, Amlodipine 116644-53-2, Mibefradil

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(calcium channel blockers plus  $\beta$ -blockers in humans with exercise-induced angina pectoris)

IT 116644-53-2, Mibefradil

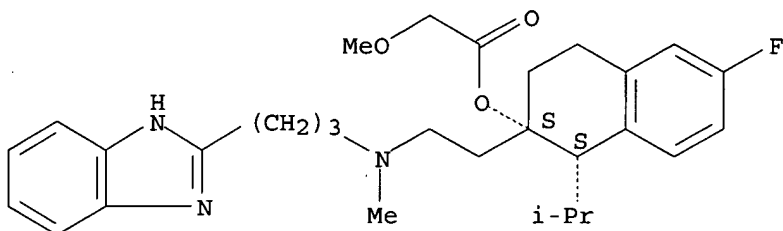
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(calcium channel blockers plus  $\beta$ -blockers in humans with exercise-induced angina pectoris)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 6 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 11

ACCESSION NUMBER: 1999:717185 HCAPLUS

DOCUMENT NUMBER: 132:202834

TITLE: Contrasting effects of selective T- and L-type calcium channel blockade on glomerular damage in DOCA hypertensive rats

AUTHOR(S): Karam, Habib; Clozel, Jean-Paul; Bruneval, Patrick; Gonzalez, Marie-Francoise; Menard, Joel

CORPORATE SOURCE: INSERM U367, Paris, F-75005, Fr.

SOURCE: Hypertension (1999), 34(4, Pt. 1), 673-678

CODEN: HPRTDN; ISSN: 0194-911X

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 10 Nov 1999

AB Mibefradil and Amlodipine are calcium antagonists with different channel selectivities. Mibefradil blocks both L- and T-type calcium channels although, in the usual pharmacol. doses, it predominantly blocks the T-type channels. In contrast, Amlodipine selectively blocks L-type channels. The goal of the present study was to assess whether this

differential selectivity would result in different effects on end-organ damage in exptl. hypertension. For this purpose, deoxycorticosterone acetate (DOCA)-salt hypertensive rats were treated either with equipotent doses of Mibefradil or Amlodipine (30 mg·kg<sup>-1</sup>·d<sup>-1</sup> as food admix). Despite the fact that both drugs decreased systolic arterial pressure to the same extent (140 ± 5 mm Hg in the Mibefradil group and 144 ± 3 mm Hg in the Amlodipine group vs. 225 ± 5 mm Hg in the untreated-DOCA group), only Mibefradil decreased proteinuria (35.5 ± 6.5 vs. 103.3 ± 14.1 mg/24 h in untreated DOCA-salt animals) and prevented glomerular lesions. Both drugs, however, prevented the occurrence of vascular renal lesions. To elucidate the mechanism responsible for this difference, the authors evaluated in an addnl. series of expts. the effects of Mibefradil and Amlodipine on plasma and renal renin concns., as well as the effects of the addition of Enalapril, an ACE inhibitor, given on top of both drugs on proteinuria. Amlodipine, in contrast to Mibefradil, markedly stimulated the plasma (17.8 ± 2.6 ng Ang I·mL<sup>-1</sup>·h<sup>-1</sup> in the Amlodipine group vs. 3.9 ± 0.4 ng Ang I·mL<sup>-1</sup>·h<sup>-1</sup> in the Mibefradil group and 3.2 ± 0.3 ng Ang I·mL<sup>-1</sup>·h<sup>-1</sup> in the untreated-DOCA group) and renal (2.42 ± 0.37 ng Ang I·mL<sup>-1</sup>·h<sup>-1</sup> in the Amlodipine group vs. 0.36 ± 0.04 ng Ang I·mL<sup>-1</sup>·h<sup>-1</sup> in the Mibefradil group and 0.26 ± 0.08 ng Ang I·mL<sup>-1</sup>·h<sup>-1</sup> in the untreated-DOCA group) renin concns. Stimulation of the renin-angiotensin system could explain the absence of a renal protective effect of Amlodipine. This was also suggested by the fact that Enalapril given in addition to Amlodipine could decrease proteinuria. Thus, T-type channel blockade by Mibefradil decreases blood pressure without stimulation of the renin-angiotensin system and therefore prevents most of the glomerular damage in DOCA hypertensive rats.

CC 1-8 (Pharmacology)

IT 88150-42-9, Amlodipine **116644-53-2**, Mibefradil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(contrasting effects of selective T- and L-type **calcium channel** blockade on glomerular damage in DOCA hypertensive rats)

IT **116644-53-2**, Mibefradil

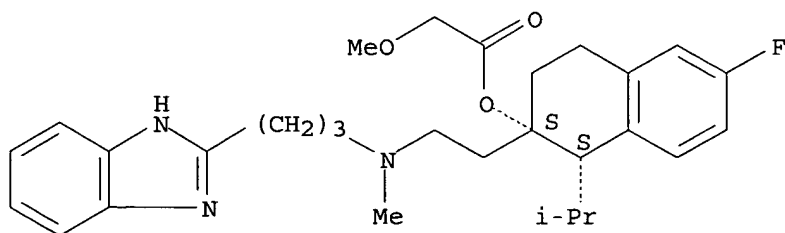
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(contrasting effects of selective T- and L-type **calcium channel** blockade on glomerular damage in DOCA hypertensive rats)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 7 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 16

ACCESSION NUMBER: 1998:477630 HCAPLUS

DOCUMENT NUMBER: 129:254666

TITLE: Effects of mibefradil, a novel calcium channel blocking agent with T-type activity, in acute experimental myocardial ischemia: maintenance of ventricular fibrillation threshold without inotropic compromise

AUTHOR(S): Muller, Cecilia A.; Opie, Lionel H.; Mccarthy, Joy; Hofmann, Dirk; Pineda, Carlos A.; Peisach, Max

CORPORATE SOURCE: Medical Research Council Heart Research Group, Cape Heart Centre, University of Cape Town, Cape Town, 7925, S. Afr.

SOURCE: Journal of the American College of Cardiology ( 1998), 32(1), 268-274

CODEN: JACCDI; ISSN: 0735-1097

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 03 Aug 1998

AB We tested whether mibefradil, a selective T-type calcium channel blocking agent, could differentially inhibit exptl. ventricular arrhythmogenesis more than contractility during acute regional ischemia and reperfusion compared with that during L-channel blockade by verapamil. T-type calcium channels are found in nodal and conduction tissue and in vascular smooth muscle, but in much lower d. in contractile myocardium. The potential role of mibefradil in ventricular arrhythmogenesis remains unclear. Mibefradil (Ro 40-5967, 1 mg/kg body weight i.v. [IV]) was given as a bolus 30 min before anterior descending coronary artery ligation, followed by 2 mg/kg per h IV during 20 min of ischemia and 25 min of reperfusion in open chest pigs. In a second group, mibefradil was given in a dose twice as high. A third group received verapamil (0.3 mg/kg IV), followed by an infusion of 0.6 mg/kg per h. During the ischemic period, the low (clin. relevant) dose of mibefradil prevented the fall of the ventricular fibrillation threshold, without depressing the maximal rate of pressure development of the left ventricle (LVmax dp/dt). This low dose increased left ventricular blood flow, whereas peripheral arterial pressure remained unchanged. The higher dose of both mibefradil and verapamil was antiarrhythmic during ischemia, at the cost of depressed contractile activity. During reperfusion, only the higher dose of mibefradil and verapamil was antiarrhythmic but both depressed contractile activity. Mibefradil is antiarrhythmic, without inotropic compromise. Speculatively, both T-type and L-type calcium channel blockade are involved in these effects.

CC 1-8 (Pharmacology)

IT 116644-53-2, Mibefradil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(antiarrhythmic effects of mibefradil, T-type calcium channel blocker, without inotropic compromise)

IT 116644-53-2, Mibefradil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

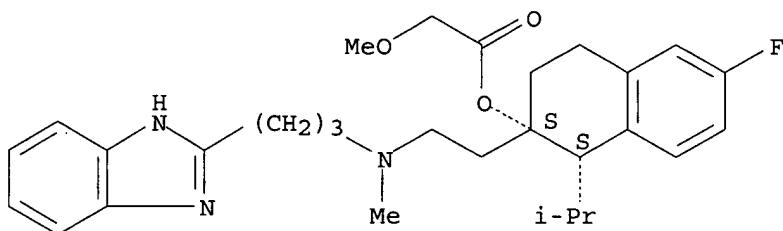
(antiarrhythmic effects of mibefradil, T-type calcium

channel blocker, without inotropic compromise)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 8 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 17

ACCESSION NUMBER: 1998:333488 HCAPLUS

DOCUMENT NUMBER: 129:49098

TITLE: Mibefradil, a T-type channel-selective calcium antagonist: clinical trials in chronic stable angina pectoris

AUTHOR(S): Massie, Barry M.

CORPORATE SOURCE: University of California, San Francisco, CA, USA

SOURCE: American Journal of Hypertension (1998), 11(4, Pt. 3), 95S-102S

CODEN: AJHYE6; ISSN: 0895-7061

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 04 Jun 1998

AB A review with 31 refs. Pharmacotherapy with nitrates,  $\beta$ -blockers, and calcium antagonists is the cornerstone of management of patients with chronic stable angina pectoris. While these agents are all effective, their use may be limited by pharmacol. tolerance, side effects, and drug interactions. Mibefradil is a recently developed calcium antagonist with a unique chemical structure, pharmacol. profile, and mode of action. Unlike all previously available calcium antagonists, mibefradil acts primarily by selective blockade of T-type calcium channels, rather than L-type channels, at clin. relevant concns. It has been evaluated as a treatment for angina in placebo-controlled and active-controlled clin. trials. Treatment with 50 mg mibefradil resulted in a significant improvement in exercise tolerance test duration in three of the five placebo-controlled trials, and a significant improvement in time to onset of angina in two of the five trials. Time to onset of ischemia as evaluated by 0.1 mV ST-segment depression was increased in all five placebo-controlled trials. Treatment with 100 mg mibefradil resulted in significant improvement in all three exercise tolerance test parameters in all studies. Mibefradil further improved exercise tolerance test duration and other efficacy parameters when administered concomitantly to patients on background  $\beta$ -blocker or nitrate therapy. In addition, treatment with mibefradil was associated with a dose-dependent decrease in heart rate, double product, frequency of anginal attacks, nitroglycerin consumption, and both frequency and duration of silent ischemic episodes. In comparative trials, 100 mg mibefradil once daily was superior in efficacy to 10 mg



amlodipine once daily and was at least equivalent to diltiazem in both efficacy and tolerability. Mibefradil was safe and well tolerated in all studies.

CC 1-0 (Pharmacology)

IT 116644-53-2, Mibefradil

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(T-type **channel-selective calcium** antagonist  
mibefradil treatment of humans with chronic stable **angina**  
pectoris)

IT 116644-53-2, Mibefradil

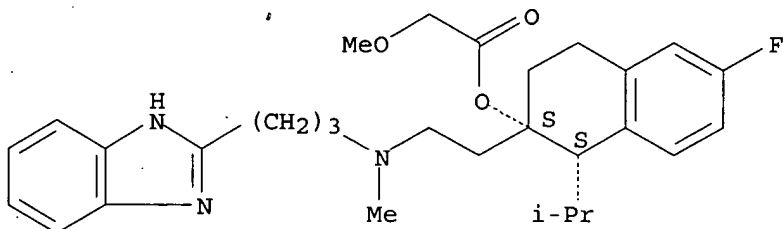
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(T-type **channel-selective calcium** antagonist  
mibefradil treatment of humans with chronic stable **angina**  
pectoris)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 9 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 19

ACCESSION NUMBER: 1998:333487 HCAPLUS

DOCUMENT NUMBER: 129:49097

TITLE: Mibefradil, a T-channel-selective calcium antagonist: clinical trials in hypertension

AUTHOR(S): Oparil, Suzanne

CORPORATE SOURCE: University of Alabama at Birmingham, Birmingham, AL, 35294, USA

SOURCE: American Journal of Hypertension (1998), 11(4, Pt. 3), 88S-94S  
CODEN: AJHYE6; ISSN: 0895-7061

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 04 Jun 1998

AB A review with 30 refs. Mibefradil, a tetralol derivative, is the first representative of a new class of calcium antagonists. It selectively blocks entry of calcium into cells through T-type channels. The efficacy and tolerability of mibefradil in the treatment of mild-to-moderate essential hypertension were evaluated in four placebo-controlled, double-blind, dose-finding studies involving over 1000 patients. Two trials involved patients from the general population, one examined a

CC 1-0 (Pharmacology)

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(T-channel-selective **calcium** antagonist mibefradil treatment of humans with **hypertension**)

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(T-channel-selective calcium antagonist mibefradil treatment of humans with hypertension)

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Chemical structure of compound 10: A benzimidazole ring system connected via a  $(\text{CH}_2)_3$  chain to a nitrogen atom. This nitrogen is also bonded to a methyl group and a 4-(4-fluorophenyl)-2-methyl-2,3-dihydro-1,4-benzodithiine-5-yl group. The benzodithiine ring has a methoxycarbonyl group at position 2 and an isopropyl group at position 3.

AUTHOR(S) : Kobrin, Isaac; Bieska, Gabriele; Charlton, Vincent;  
Lindberg, Elisabet; Pordy, Robert

CORPORATE SOURCE: Roche Laboratories, Clinical Research, Nutely, NJ,  
07110, USA

SOURCE: Cardiology (1998), 89(Suppl. 1), 23-32  
CODEN: CAGYAO; ISSN: 0008-6312

PUBLISHER: S. Karger AG

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 25 Apr 1998

AB A review with 28 refs. Mibefradil is the first of a new class of calcium antagonists (CAs), the tetralol derivs., that selectively blocks the T-type calcium channel. The anti-anginal and anti-ischemic efficacy of mibefradil in patients with chronic stable angina pectoris was established in five placebo-controlled trials (2 monotherapy trials, 3 trials with background  $\beta$ -blocker or long-acting nitrate therapy). At the recommended doses of 50 and 100 mg, mibefradil treatment was associated with a significant dose-related increase in exercise test variables regardless of demog. subpopulation or background therapy. Significant redns. in weekly anginal attacks, silent ischemic parameters, heart rate (HR) and rate-pressure product were also observed. Two active-controlled trials compared mibefradil 100 mg with amlodipine 10 mg or diltiazem SR 120 mg b.i.d., resp. Patients receiving mibefradil showed significantly larger improvements than did those treated with amlodipine and similar improvements as those treated with diltiazem SR in all variables measured. In both studies, treatment with mibefradil was associated with a greater decrease in HR and rate-pressure product. Mibefradil was well tolerated and safe; this held true for patients on chronic anti-anginal background therapy. The overall incidences of adverse events and premature withdrawals were only slightly higher than those of placebo-treated patients. Asymptomatic sin-us bradycardia and first-degree atrioventricular block were the most frequently occurring mibefradil dose-related ECG changes. Mibefradil was better tolerated than amlodipine (mainly with regard to leg edema) and similarly well tolerated as diltiazem CD.

CC 1-0 (Pharmacology)

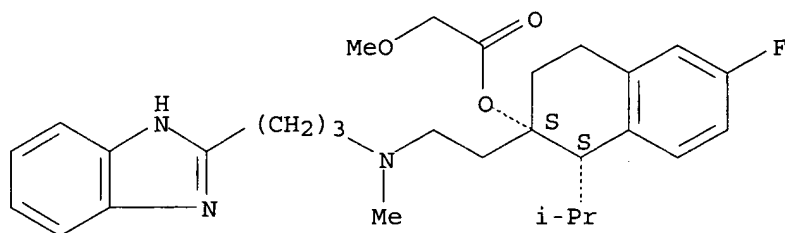
IT 116644-53-2, Mibefradil  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(anti-anginal and anti-ischemic effects of mibefradil, a new T-type calcium channel antagonist)

IT 116644-53-2, Mibefradil  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(anti-anginal and anti-ischemic effects of mibefradil, a new T-type calcium channel antagonist)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 11 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 25

ACCESSION NUMBER: 1997:669703 HCAPLUS

DOCUMENT NUMBER: 127:314598

TITLE: Long-term antianginal and antiischemic effects of mibefradil, the novel T-type calcium channel blocker: a multicenter, double-blind, placebo-controlled, randomized comparison with sustained-release diltiazem

AUTHOR(S): Davies, Graham J.; Kobrin, Isaac; Caspi, Abraham; Reisin, Leonardo H.; De Albuquerque, Denilson Campos; Armagnijan, Dikran; Coelho, Otavio Rizzi; Schneeweiss, Adam

CORPORATE SOURCE: Royal Postgraduate Medical School, Hammersmith Hospital, London, W12 0SH, UK

SOURCE: American Heart Journal (1997), 134(2, Pt. 1), 220-228

CODEN: AHJOA2; ISSN: 0002-8703

PUBLISHER: Mosby-Year Book

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 22 Oct 1997

AB This study compared the efficacy, safety, and tolerability of mibefradil to sustained-release diltiazem in patients with chronic stable angina pectoris. At week 12, statistically equivalent mean increases in exercise tolerance test (ETT) duration of > 1 min were observed in both groups. Similar improvements in time to onset of angina and time to persistent 1 mm ST-segment depression were also observed with both drugs. Large redns. in heart rate, blood pressure, and rate-pressure product were observed at each stage of the ETT among patients treated with mibefradil. Each drug was associated with at least a 70% reduction from baseline in anginal frequency and nitroglycerin consumption. Patients maintained on mibefradil during the withdrawal period had significant increases in all three ETT variables at week 16 compared with placebo. The effectiveness of mibefradil is comparable with sustained-release diltiazem in treating chronic stable angina pectoris, although mibefradil provides greater redns. in heart rate and cardiac workload.

CC 1-8 (Pharmacology)

IT 42399-41-7, Diltiazem 116644-53-2, Mibefradil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(comparison of mibefradil, the novel T-type calcium channel blocker with diltiazem in the treatment of angina and myocardial ischemia in humans)

IT 116644-53-2, Mibefradil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

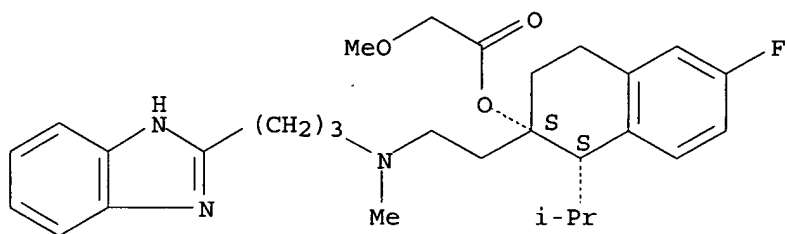
## (Uses)

(comparison of mibefradil, the novel T-type calcium channel blocker with diltiazem in the treatment of angina and myocardial ischemia in humans)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 12 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 26

ACCESSION NUMBER: 1997:234499 HCAPLUS

DOCUMENT NUMBER: 126:301570

TITLE: Cardiovascular alterations in rat fetuses exposed to calcium channel blockers

AUTHOR(S): Scott, William J., Jr.; Resnick, Elisabeth; Hummler, Hans; Clozel, Jean-Paul; Buergin, Heinrich

CORPORATE SOURCE: Division of Developmental Biology, Children's Hospital Research Foundation, Cincinnati, OH, 45229-3039, USA

SOURCE: Reproductive Toxicology (1997), 11(2/3), 207-214

CODEN: REPTED; ISSN: 0890-6238

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 11 Apr 1997

AB Preclin. toxicol. investigation suggested that a new calcium channel blocker, Ro 40-5967, induced cardiovascular alterations in rat fetuses exposed to this agent during organogenesis. The present study was designed to investigate the hypothesis that calcium channel blockers in general induce cardiovascular malformations indicating a pharmacol. class effect. The authors studied three calcium channel blockers of different structure, nifedipine, diltiazem, and verapamil, along with the new agent. Pregnant rats were administered one of these calcium channel blockers during the period of cardiac morphogenesis and the offspring examined on day 20 of gestation for a cardiovascular malformations. A low incidence of cardiovascular malformations was observed after exposure to each of the calcium channel blockers, but this incidence was statistically significant only for verapamil and nifedipine. All four agents were associated with aortic arch branching variants, although significantly increased only for Ro 40-5967 and verapamil.

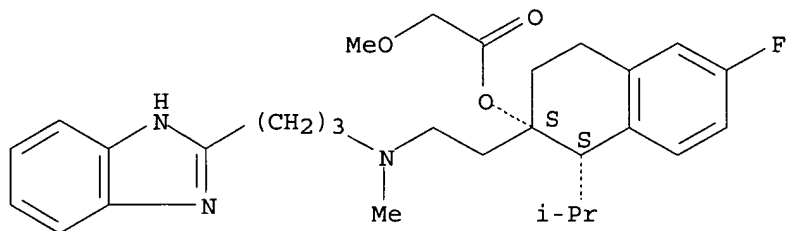
CC 1-8 (Pharmacology)

IT 52-53-9, Verapamil 21829-25-4, Nifedipine 42399-41-7, Diltiazem 116666-63-8, Ro 40-5967

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (cardiovascular alterations in rat fetuses exposed to

calcium channel blockers)  
 IT 116666-63-8, Ro 40-5967  
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)  
 (cardiovascular alterations in rat fetuses exposed to  
 calcium channel blockers)  
 RN 116666-63-8 HCAPLUS  
 CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 HCl

L103 ANSWER 13 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 27  
 ACCESSION NUMBER: 1996:28720 HCAPLUS  
 DOCUMENT NUMBER: 124:106113  
 TITLE: Mechanism of the antiischemic effect of mibefradil, a selective T calcium channel blocker in dogs: comparison with amlodipine  
 AUTHOR(S): Roux, Sebastien; Buehler, Manfred; Clozel, Jean-Paul  
 CORPORATE SOURCE: Pharma Division, F. Hoffmann-La Roche Ltd., Basel, CH-4002, Switz.  
 SOURCE: Journal of Cardiovascular Pharmacology (1996), 27(1), 132-9  
 CODEN: JCPCDT; ISSN: 0160-2446  
 PUBLISHER: Lippincott-Raven  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 ED Entered STN: 13 Jan 1996  
 AB Calcium channel blockers are active in variant angina principally by preventing coronary vasospasm. However, a direct antiischemic effect may also occur. In open-chest dogs, an attack of variant angina was mimicked by a 2-min critical coronary stenosis and the following reversible myocardial ischemia was assessed by measuring the decrease of segmental shortening. The authors compared the antiischemic mechanism of mibefradil, a T and L calcium channel blocker with that of amlodipine, a pure L channel blocker. Both drugs showed a similar relation between the decrease of the rate-pressure product and the antiischemic effect, but only mibefradil reduced heart rate. Amlodipine and mibefradil at the highest doses tested (20 and 70 µg/kg/min, resp.) restored 68 and 76% of segmental shortening in the ischemic area, resp., as compared with preischemic values. Matching blood pressure (by intraaortic balloon) or heart rate (by atrial pacing) to predrug values showed that the antiischemic effect was mainly afterload-dependent for amlodipine and heart rate-dependent for mibefradil. The authors conclude that in variant angina, in addition to

their antivasospastic effects, calcium channel blockers may be antiischemic by a direct myocardial effect associated with a decrease of the rate pressure product. Blockade of the T channel does not seem to participate in the direct antiischemic effect of mibefradil but could explain the decrease of heart rate.

CC 1-8 (Pharmacology)

IT 88150-42-9, Amlodipine 116644-53-2, Mibefradil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(mechanism of the **antiischemic** effect of mibefradil, a selective T **calcium channel** blocker in dogs: comparison with amlodipine)

IT 116644-53-2, Mibefradil

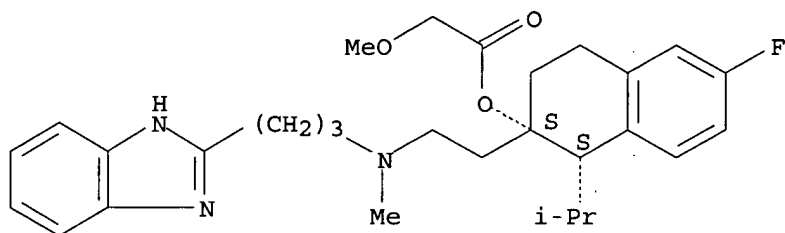
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(mechanism of the **antiischemic** effect of mibefradil, a selective T **calcium channel** blocker in dogs: comparison with amlodipine)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 14 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 29

ACCESSION NUMBER: 1994:69113 HCAPLUS

DOCUMENT NUMBER: 120:69113

TITLE: Effects of calcium channel blockade on the aortic intima in spontaneously hypertensive rats

AUTHOR(S): Gray, Gillian A.; Clozel, Martine; Clozel, Jean Paul; Baumgartner, Hans Rudolf

CORPORATE SOURCE: Preclin. Res. Dep., F. Hoffmann-La Roche Ltd., Basel, CH-4002, Switz.

SOURCE: Hypertension (1993), 22(4), 569-76

CODEN: HPRTDN; ISSN: 0194-911X

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 19 Feb 1994

AB Hypertension is associated with an intimal dysfunction characterized by endothelium-dependent constriction to serotonin, decreased endothelium-dependent relaxation to acetylcholine, and a subendothelial infiltration of monocyte-macrophages. The goal of the authors' study was to evaluate the effect of long-term calcium channel blockade with Ro 40-5967, a new long-acting calcium channel blocker, on these alterations in aortas of spontaneously hypertensive rats (SHR). Arterial blood pressure was decreased by Ro 40-5967. In aortas from Ro 40-5967-treated

SHR, the serotonin ratio (maximal contraction to serotonin on rings with endothelium over maximal contraction on paired rings without endothelium) was reduced ( $1.14 \pm 0.10$ ) compared with control SHR ( $1.72 \pm 0.12$ ,  $P < .01$ ) because of inhibition of maximal contraction in rings with endothelium. This effect of Ro 40-5967 was partially reversed by an inhibitor of nitric oxide (NO) synthase, NG-nitro-L-arginine-Me ester, and partially inhibited in the presence of the thromboxane/prostaglandin H2 receptor antagonist AH 23848. Maximal relaxation to acetylcholine in rings with endothelium was increased by Ro 40-5967. In rings without endothelium, Ro 40-5967 treatment enhanced the sensitivity to sodium nitroprusside-induced relaxation. Cyclic GMP content, an indicator of NO release, was not increased in aortas from Ro 40-5967-treated SHR. Thus, improvement of endothelial function was probably achieved by facilitating the action of NO at the level of the smooth muscle cells and by reducing prostaglandin H2-induced constriction. Finally, the number of monocyte-macrophages in the subendothelium was decreased by Ro 40-5967. The authors conclude that long-term treatment with Ro 40-5967 reverses both the functional and morphol. changes of the aortic intima in hypertension.

CC 1-8 (Pharmacology)

IT 116666-63-8

RL: BIOL (Biological study)

(as **calcium channel** blocker, endothelial and  
intimal aortic changes response to, **antihypertensive** activity  
in relation to)

IT 116666-63-8

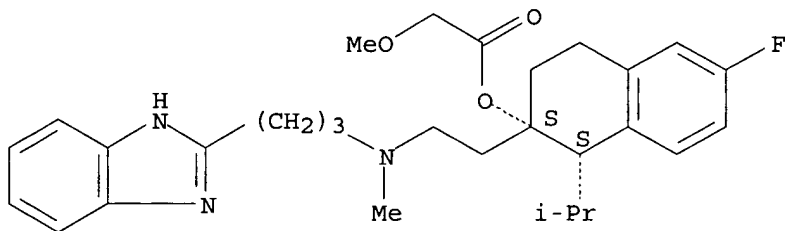
RL: BIOL (Biological study)

(as **calcium channel** blocker, endothelial and  
intimal aortic changes response to, **antihypertensive** activity  
in relation to)

RN 116666-63-8 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 HCl

L103 ANSWER 15 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:25483 HCAPLUS

DOCUMENT NUMBER: 137:119323

TITLE: Comparison of L-type and mixed L- and T-type calcium  
channel blockers on kidney injury caused by  
deoxycorticosterone-salt hypertension in rats

AUTHOR(S): Baylis, Chris; Qiu, Changbin; Engels, Kevin



CORPORATE SOURCE: Department of Physiology, West Virginia University  
Health Sciences Center, Morgantown, WV, 26506-9229,  
USA

SOURCE: American Journal of Kidney Diseases (2001),  
38(6), 1292-1297

CODEN: AJKDDP; ISSN: 0272-6386

PUBLISHER: W. B. Saunders Co.

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 10 Jan 2002

AB The efficiency of calcium channel blockers (CCBs) in the treatment of chronic renal disease (CRD) is controversial. In this study, we investigated whether combined T- and L-type CCBs, using mibefradil (30 mg/kg/day), provided superior protection vs. traditional L-type voltage-gated CCBs, using amlodipine (10 mg/kg/day), in the deoxycorticosterone acetate (DOCA)-salt model of high glomerular blood pressure (PGC) and rapidly developing kidney damage. After 4 to 5 wk of DOCA-salt, amlodipine did not reduce proteinuria (protein,  $341 \pm 90$  vs.  $482 \pm 54$  mg/24 h;  $P =$  not significant) or degree of glomerular damage ( $20\% \pm 4\%$  vs.  $28\% \pm 6\%$  damaged glomeruli;  $P =$  not significant) compared with untreated rats. Conversely, mibefradil reduced proteinuria and glomerular damage vs. untreated DOCA-salt rats (protein,  $244 \pm 75$  mg/24 h;  $P < 0.02$ ; damaged glomeruli,  $11\% \pm 3\%$ ;  $P < 0.05$ ). Both CCBs had similar antihypertensive actions, returning blood pressure to the untreated sham value. Of note, PGC also was reduced by a similar extent (and to the sham value) with both mibefradil ( $58 \pm 2$  mm Hg;  $P < 0.001$ ) and amlodipine ( $61 \pm 2$  mm Hg;  $P < 0.005$ ) vs. untreated DOCA-salt rats ( $70 \pm 1$  mm Hg). This study shows that combined T- and L-type CCBs provide superior protection against CRD in the DOCA-salt model compared with L-type CCBs alone. However, this protection was not hemodynamic because similar systemic and glomerular antihypertensive responses occurred with both mibefradil and amlodipine. Although mibefradil was withdrawn from the market because of adverse drug interactions not associated with CCBs, other mixed channel blockers may provide an alternative or adjunctive therapy to angiotensin-converting enzyme inhibition in CRD.

CC 1-8 (Pharmacology)

IT 88150-42-9, Amlodipine **116644-53-2**, Mibefradil

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(comparison of L-type and mixed L- and T-type **calcium channel** blockers on kidney injury caused by deoxycorticosterone-salt **hypertension** in rats)

IT **116644-53-2**, Mibefradil

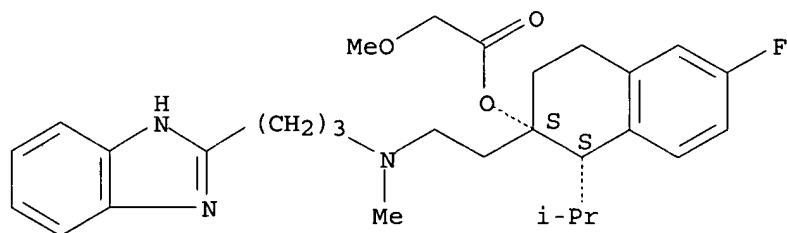
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(comparison of L-type and mixed L- and T-type **calcium channel** blockers on kidney injury caused by deoxycorticosterone-salt **hypertension** in rats)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 16 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:379018 HCAPLUS

DOCUMENT NUMBER: 135:175004

TITLE: Inhibition of T-type and L-type calcium channels by mibefradil: physiologic and pharmacologic bases of cardiovascular effects

AUTHOR(S): Leuranguer, Valerie; Mangoni, Matteo E.; Nargeot, Joel; Richard, Sylvain

CORPORATE SOURCE: Institute of Human Genetics, Montpellier, Fr.

SOURCE: Journal of Cardiovascular Pharmacology (2001), 37(6), 649-661

CODEN: JCPCDT; ISSN: 0160-2446

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 25 May 2001

AB Ca<sup>2+</sup> channel antagonists of the dihydropyridine, benzothiazepine, and phenylalkylamine classes have selective effects on L-type vs. T-type Ca<sup>2+</sup> channels. In contrast, mibefradil was reported to be more selective for T-type channels. We used the whole-cell patch-clamp technique to investigate the effects of mibefradil on T-type and L-type Ca<sup>2+</sup> currents (ICaT and ICaL) recorded at physiol. extracellular Ca<sup>2+</sup> in different cardiac cell types. At a stimulation rate of 0.1 Hz, mibefradil blocked ICaT evoked from neg. holding potentials (HPs) (-100 mV to -80 mV) with an IC<sub>50</sub> of 0.1 μM in rat atrial cells. This concentration had no effect on ICaL in rat ventricular cells (IC<sub>50</sub>: .apprx.3 μM). However, block of ICaL was enhanced when the HP was depolarized to -50 mV (IC<sub>50</sub>: .apprx.0.1 μM). Besides a resting block, mibefradil displayed voltage- and use-dependent effects on both ICaT and ICaL. In addition, inhibition was enhanced by increasing the duration of the step-depolarizations. Similar effects were observed in human atrial and rabbit sinoatrial cells. In conclusion, mibefradil combines the voltage- and use-dependent effects of dihydropyridines and benzothiazepines on ICaL. Inhibition of ICaL, which has probably been underestimated before, may contribute to most of the cardiovascular effects of mibefradil.

CC 1-8 (Pharmacology)

IT 116644-53-2, Mibefradil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(mibefradil inhibition of T- and L-type calcium channels: cardiovascular action mechanism)

IT 116644-53-2, Mibefradil

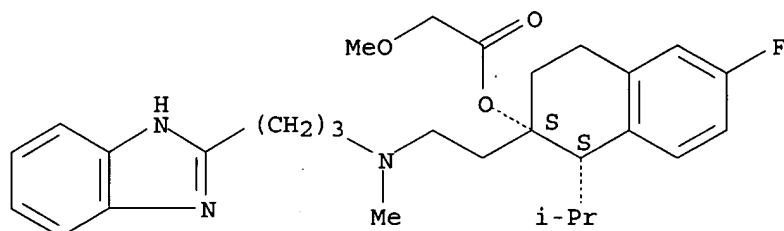
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(mibefradil inhibition of T- and L-type calcium channels: cardiovascular action mechanism)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 17 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:286846 HCAPLUS

DOCUMENT NUMBER: 135:205221

TITLE: Effects of the T-type calcium channel blockade with oral mibefradil on the electrophysiologic properties of the human heart

AUTHOR(S): Madle, Alois; Linhartova, Katerina; Koza, Jiri  
CORPORATE SOURCE: 2nd Department of Medicine, University Hospital, Plzen, 30599, Czech Rep.

SOURCE: Medical Science Monitor (2001), 7(1), 74-77  
CODEN: MSMOFR; ISSN: 1234-1010

PUBLISHER: Medical Science International Publishing

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 23 Apr 2001

AB As the calcium T-channel blockade is a new pharmacol. category with presumably unique electrophysiol. effects, the influence of its only representative yet mibefradil was tested after the single oral dose. 10 Patients underwent the electrophysiol. examination. Normal baseline values in sinus node cycle length (SNCL), sinus node recovery time (SNRT), corrected sinus node recovery time (CSNRT), PA interval, atrial effective refractory period, AH interval, Wenckebach point (WP), atrioventricular nodal refractory period, and HV interval were measured using standard techniques. After that a single dose of 100 mg mibefradil was given and the testing repeated in 90 min. Though non-significantly in a study-group limited in size due to global withdrawal of mibefradil, sinus node automaticity was suppressed (prolongation of SNRT by 5.1% and CSNRT by 11.5%) and heart rate lowered (SNCL prolonged by 2.8%) comparatively more than was the neg. dromotropic effect on the atrioventricular node (negligible prolongation of AH interval by 1.1% and WP cycle by 0.4%). Demonstrated electrophysiol. effects of oral mibefradil with more pronounced influence on the automaticity of the sinus node seem to be in agreement with the preclin. data on the predominant role of T-channels in the pacemaker activity of the sinus node. According to the Framingham data on the risk of heart rate for the cardiovascular as well as all-cause mortality, calcium T-channel blockade offers a desirable profile for antihypertensive treatment. From this point of view development of new representatives of calcium T-channel blockers could be a useful contribution to clin.

practice.

CC 1-8 (Pharmacology)

IT **116644-53-2**, Mibefradil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(effects of oral mibefradil, T-type **calcium channel** blocker, on electrophysiol. properties of human **heart**)

IT **116644-53-2**, Mibefradil

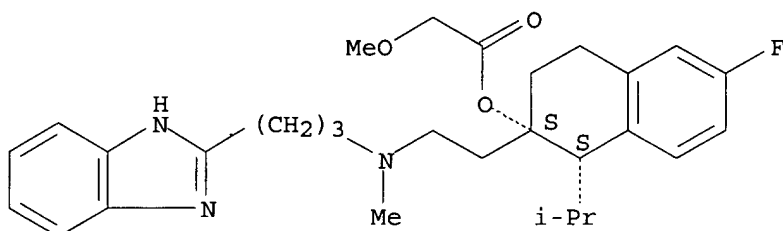
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(effects of oral mibefradil, T-type **calcium channel** blocker, on electrophysiol. properties of human **heart**)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 18 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:20655 HCAPLUS

DOCUMENT NUMBER: 134:217015

TITLE: Calcium channel blockade limits cardiac remodeling and improves cardiac function in myocardial infarction-induced heart failure in rats

AUTHOR(S): Sandmann, Steffen; Claas, Ralf; Cleutjens, Jack P. M.; Daemen, Mat J. A. P.; Unger, Thomas

CORPORATE SOURCE: Institute of Pharmacology, Christian-Albrechts-University of Kiel, Kiel, 24105, Germany

SOURCE: Journal of Cardiovascular Pharmacology (2001), 37(1), 64-77

CODEN: JCPCDT; ISSN: 0160-2446

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 10 Jan 2001

AB Calcium channel antagonists (CCAs) have been proposed to prevent cardiac events after myocardial infarction (MI). However, unwanted effects, such as neg. inotropy, limit their use in many cases. The aim of this study was to compare the effects of long-term treatment with the CCAs, mibefradil, verapamil, and amlodipine, administered before and after chronic MI on myocardial remodeling and cardiac function. MI was induced by permanent ligation of the left coronary artery in male Wistar rats. Infarcted animals were treated with placebo, mibefradil (10 mg/kg/d po), verapamil (8 mg/kg bid po), or amlodipine (4 mg/kg/d po). Treatment was

started 7 days before or 3 h after MI induction. Six weeks after MI, mean arterial blood pressure (MAP), heart rate (HR), left ventricular end diastolic pressure (LVEDP), and cardiac contractility (dP/dtmax) were measured. Morphometric parameters such as infarct size (IS), left ventricular dilation (LVD), septal thickness (ST), and cardiac fibrosis were determined in picrosirius red-stained hearts. Six weeks after MI, MAP and dP/dtmax were decreased, whereas LVEDP and HR were increased in placebo-treated controls. The hearts featured an IS of 45%, left ventricular dilation, cardiac fibrosis, and septal thinning. MAP of all CCA-treated animals was increased, whereas LVEDP was decreased and dP/dtmax increased 7-day pre- and 3-h post-MI started in mibefradil- and amlodipine-treated animals, but not in verapamil-treated animals. In contrast to amlodipine treatment, before and after MI started mibefradil and verapamil treatment decreased HR. Pretreatment with all CCA reduced IS and increased ST, whereas only mibefradil and amlodipine pretreatment prevented LVD and cardiac fibrosis. After MI started treatment with mibefradil and amlodipine reduced IS and cardiac fibrosis, and increased ST. Long-term treatment with the CCAs mibefradil, verapamil, and amlodipine reduced myocardial remodeling and improved cardiac function in MI-induced heart failure in rats.

CC 1-8 (Pharmacology)

IT 52-53-9, Verapamil 88150-42-9, Amlodipine 116644-53-2, Mibefradil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(calcium channel blockade limits cardiac remodeling and improves cardiac function in myocardial infarction-induced heart failure)

IT 116644-53-2, Mibefradil

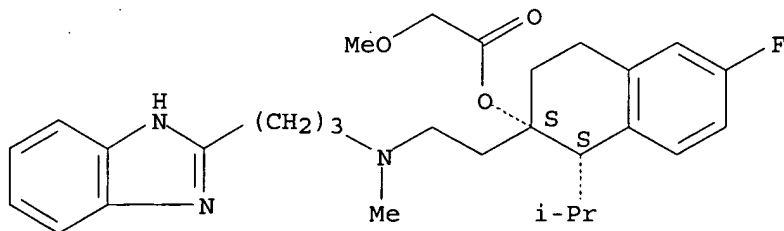
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(calcium channel blockade limits cardiac remodeling and improves cardiac function in myocardial infarction-induced heart failure)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 19 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:620008 HCAPLUS

DOCUMENT NUMBER: 136:319080

TITLE: Effects of mibefradil, a T- and L-type calcium channel

blocker, on cardiac remodeling in the UM-X7.1 cardiomyopathic hamster

AUTHOR(S): Villame, Johanne; Massicotte, Julie; Jasmin, Gaetan; Dumont, Louis

CORPORATE SOURCE: Departement de pharmacologie, Faculte de medecine, Universite de Montreal, Montreal, QC, H3C 3J7, Can.

SOURCE: Cardiovascular Drugs and Therapy (2001), 15(1), 41-48  
CODEN: CDTHET; ISSN: 0920-3206

PUBLISHER: Kluwer Academic Publishers

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 28 Aug 2001

AB Abnormalities of T-type calcium channel function reported to occur in the transition phase to heart failure in hamster cardiomyopathy may contribute to progression of the disease. This work tested the hypothesis that chronic exposure to mibefradil might improve the deleterious cardiac remodeling observed in this condition. Normal and UM-X7.1 cardiomyopathic hamsters (CMH), aged 180 days, were treated daily by gavage for 21 days with mibefradil (30 mg/kg). Animals from each group were sacrificed at the end of the treatment period, while the remainder were followed for an addnl. 30 days without treatment (washout period). Hearts were harvested, fixed with 10%-buffered paraformaldehyde and then cut in half down the middle. Several slices were dehydrated, embedded in paraffin and stained with Masson Trichrome. Wall thickness and dilatation index of the left ventricle were estimated by planimetry. Myocardial capillary d. was also computed. The greater heart weight/body weight ratio seen in untreated CMH

(7.7 vs. 5.5 in normal hamsters) was improved with mibefradil. The dilatation index which averaged 0.504 in normal animals was increased in untreated CMH (0.566) and ameliorated in mibefradil-treated CMH. The 1-mo washout period led to further deterioration of the dilatation index in untreated and mibefradil-treated CMH. Capillary d. averaged 10,000/mm<sup>2</sup> in hearts from untreated normal hamsters and 8830/mm<sup>2</sup> in untreated CMH. Chronic exposure to mibefradil reduced the capillary d. in both normal and CMH hearts. Following the 1-mo washout period, the change in myocardial capillary d. associated with mibefradil was no longer detectable. In conclusion, chronic exposure to mibefradil, a T- and L-type calcium channel blocker, exerts opposite effects during the transition phase to heart failure in CMH, improving the deleterious left ventricular remodeling in UM-X7.1 hamsters and reducing myocardial capillary d. independently of the disease process.

CC 1-8 (Pharmacology)

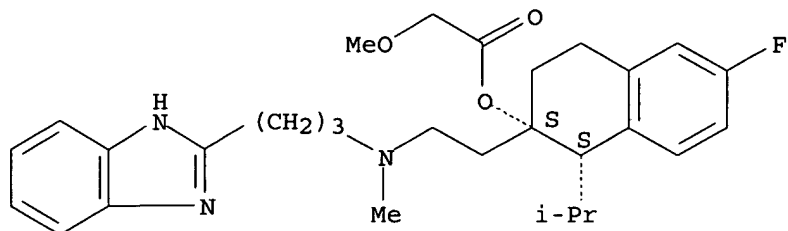
IT 116644-53-2, Mibefradil  
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(mibefradil, a **calcium channel** blocker, effects on **cardiac remodeling in the cardiomyopathic hamster**)

IT 116644-53-2, Mibefradil  
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(mibefradil, a **calcium channel** blocker, effects on **cardiac remodeling in the cardiomyopathic hamster**)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 20 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:162367 HCAPLUS

DOCUMENT NUMBER: 132:189510

TITLE: Effect of mibefradil, a T-type calcium channel blocker, on morbidity and mortality in moderate to severe congestive heart failure: the MACH-1 study  
 AUTHOR(S): Levine, T. Barry; Bernink, Peter J. L. M.; Caspi, Abraham; Elkayam, Uri; Geltman, Edward M.; Greenberg, Barry; McKenna, William J.; Ghali, Jalal K.; Giles, Thomas D.; Marmor, Alon; Reisin, Leonardo H.; Ammon, Susan; Lindberg, Elisabet

CORPORATE SOURCE: Michigan Institute for Heart Failure and Transplant Care, Botsford General Hospital, Farmington, MI, 48336, USA

SOURCE: Circulation (2000), 101(7), 758-764

CODEN: CIRCAZ; ISSN: 0009-7322

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 12 Mar 2000

AB Calcium antagonists have proved disappointing in long-term congestive heart failure (CHF) studies. Mibefradil, a new calcium antagonist that selectively blocks T-type calcium channels, has been shown to be an effective antihypertensive, antianginal, and anti-ischemic agent, and because of its different mechanism of action, it may be beneficial as adjunct therapy in CHF patients. This multicenter, randomized, double-blind study compared mibefradil with placebo as adjunct to usual therapy in 2590 CHF patients (NYHA class II to IV; left ventricular fraction <35%). The initial 50-mg daily dose of mibefradil was uptitrated to 100 mg after 1 mo and continued up to 3 yr. Patients were monitored at 1 wk; 1, 2, and 3 mo; and every 3 mo thereafter. All-cause mortality, cardiovascular mortality, and cardiovascular morbidity/mortality were analyzed by use of the log-rank test ( $\alpha=0.05$ ). Sub studies included exercise tolerance, plasma hormone and cytokines, echocardiog., and quality of life. Total mortality was similar between mibefradil- and placebo-treated patients ( $P=0.151$ ). The 14% increased risk of mortality with mibefradil in the first 3 mo was not statistically significant ( $P=0.093$ ). Treatment groups had similar cardiovascular mortality ( $P=0.246$ ), cardiovascular morbidity/mortality ( $P=0.783$ ), and reasons for death or hospitalization. Patients comedicated with mibefradil and antiarrhythmics (class I or III), including amiodarone, had a significantly increased risk of death. Sub studies demonstrated no significant differences between treatments. When used as adjunct therapy, mibefradil did not affect the usual outcome of CHF. The potential interaction with antiarrhythmic drugs, especially amiodarone, and drugs associated

with torsade de pointes may have contributed to poor outcomes early in the

study.

CC 1-8 (Pharmacology)

IT 116644-53-2, Mibefradil

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(effect of mibefradil, a T-type **calcium channel**

blocker, on morbidity and mortality in moderate to severe congestive heart failure in humans)

IT 116644-53-2, Mibefradil

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

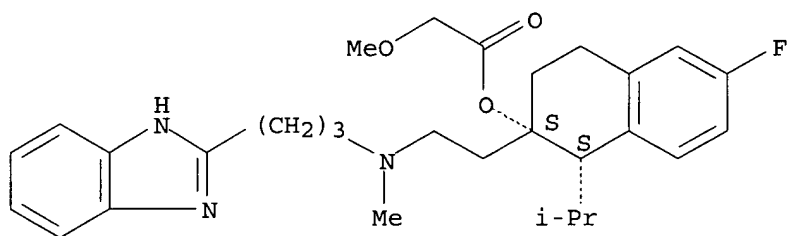
(effect of mibefradil, a T-type **calcium channel**

blocker, on morbidity and mortality in moderate to severe congestive heart failure in humans)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 21 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:405028 HCAPLUS

DOCUMENT NUMBER: 133:217516

TITLE: High affinity interaction of mibefradil with voltage-gated calcium and sodium channels

AUTHOR(S): Eller, Philipp; Berjukov, Stanislav; Wanner, Siegmund; Huber, Irene; Hering, Steffen; Knaus, Hans-Gunther; Toth, Geza; Kimball, S. David; Striessnig, Jorg

CORPORATE SOURCE: Institut fur Biochemische Pharmakologie, Innsbruck, A-6020, Austria

SOURCE: British Journal of Pharmacology (2000), 130(3), 669-677

CODEN: BJPCBM; ISSN: 0007-1188

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 20 Jun 2000

AB Mibefradil is a novel Ca<sup>2+</sup> antagonist which blocks both high-voltage activated and low voltage-activated Ca<sup>2+</sup> channels. Although L-type Ca<sup>2+</sup> channel block was demonstrated in functional expts. its mol. interaction with the channel has not yet been studied. We therefore investigated the binding of [3H]-mibefradil and a series of mibefradil analogs to L-type Ca<sup>2+</sup> channels in different tissues. [3H]-Mibefradil labeled a single class of high affinity sites on skeletal muscle L-type Ca<sup>2+</sup> channels (KD



of  $2.5 \pm 0.4$  nM,  $B_{max} = 56.4 \pm 2.3$  pmol mg<sup>-1</sup> of protein). Mibefradil (and a series of analogs) partially inhibited (+)-[3H]-isradipine binding to skeletal muscle membranes but stimulated binding to brain L-type Ca<sup>2+</sup> channels and  $\alpha_1C$ -subunits expressed in tsA201 cells indicating a tissue-specific, non-competitive interaction between the dihydropyridine and mibefradil binding domain. [3H]-Mibefradil also labeled a heterogeneous population of high affinity sites in rabbit brain which was inhibited by a series of nonspecific Ca<sup>2+</sup> and Na<sup>+</sup>-channel blockers. Mibefradil and its analog RO40-6040 had high affinity for neuronal voltage-gated Na<sup>+</sup>-channels as confirmed in binding (apparent  $K_i$  values of 17 and 1.0 nM, resp.) and functional expts. (40% use-dependent inhibition of Na<sup>+</sup>-channel current by 1  $\mu$ M mibefradil in GH3 cells). Our data demonstrate that mibefradil binds to voltage-gated L-type Ca<sup>2+</sup> channels with very high affinity and is also a potent blocker of voltage-gated neuronal Na<sup>+</sup>-channels. More lipophilic mibefradil analogs may possess neuroprotective properties like other nonselective Ca<sup>2+</sup>-/Na<sup>+</sup>-channel blockers.

CC 1-8 (Pharmacology)

IT 133011-25-3, Ro 19-9495 291307-58-9, Ro 19-8287  
291307-59-0, Ro 19-8531 291307-60-3, Ro 40-0293  
291307-61-4, Ro 40-0713 291307-62-5, Ro 40-6040  
291307-63-6, Ro 40-6088

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(high affinity interaction of mibeadil with voltage-gated calcium and sodium channels)

IT 116644-53-2, Mibefradil 291307-56-7, Ro 18-5881  
291307-57-8, Ro 19-6945

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(high affinity interaction of mibefradil with voltage-gated calcium and sodium channels)

IT 133011-25-3, Ro 19-9495 291307-58-9, Ro 19-8287  
291307-59-0, Ro 19-8531 291307-60-3, Ro 40-0293  
291307-61-4, Ro 40-0713 291307-63-6, Ro 40-6088

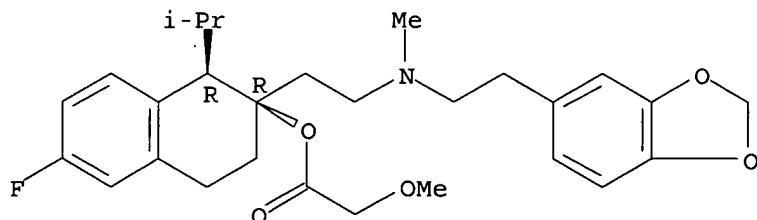
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(high affinity interaction of mibeadil with voltage-gated calcium and sodium channels)

RN 133011-25-3 HCAPLUS

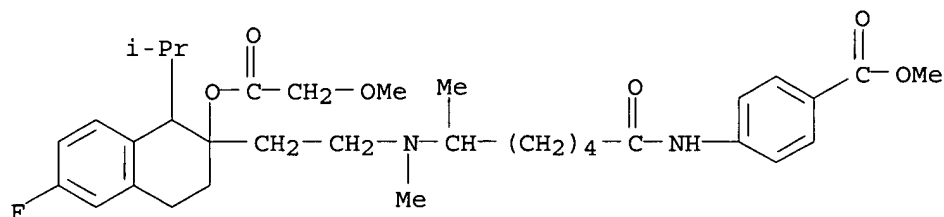
CN Acetic acid, methoxy-, (1R,2R)-2-[2-[[2-(1,3-benzodioxol-5-yl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 291307-58-9 HCAPLUS

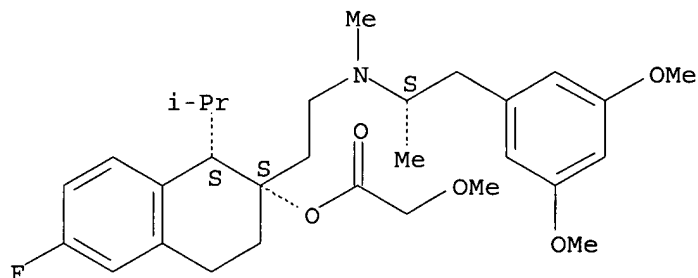
CN Benzoic acid, 4-[[6-[[2-[6-fluoro-1,2,3,4-tetrahydro-2-[(methoxyacetyl)oxy]-1-(1-methylethyl)-2-naphthalenyl]ethyl]methylamino]-1-oxoheptyl]amino]-, methyl ester (9CI) (CA INDEX NAME)



RN 291307-59-0 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[[(1S)-2-(3,5-dimethoxyphenyl)-1-methylethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

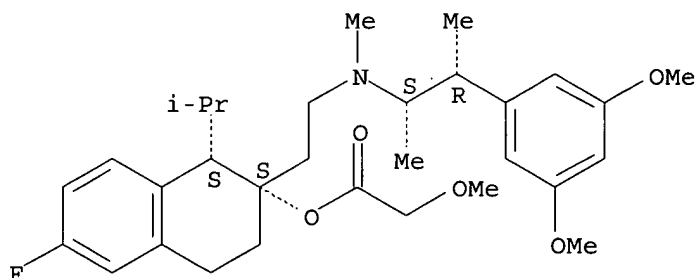
Absolute stereochemistry.



RN 291307-60-3 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[[(1S,2R)-2-(3,5-dimethoxyphenyl)-1-methylpropyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

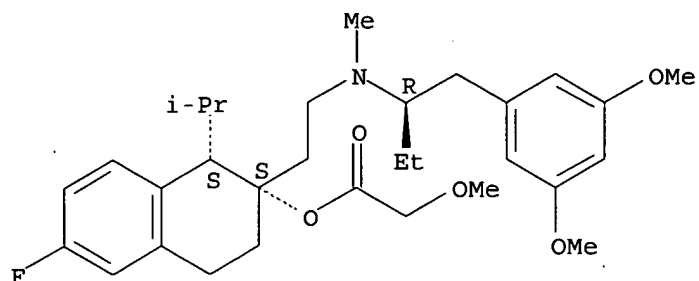
Absolute stereochemistry.



RN 291307-61-4 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[[(1R)-1-[(3,5-dimethoxyphenyl)methyl]propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

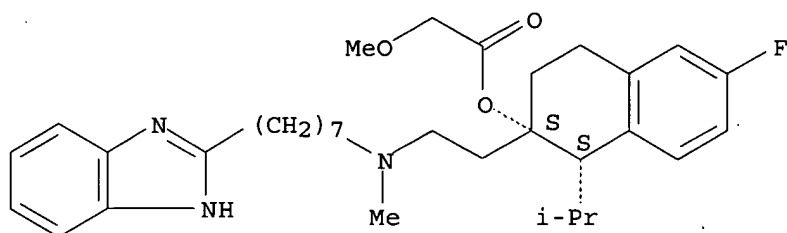
Absolute stereochemistry.



RN 291307-63-6 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[7-(1H-benzimidazol-2-yl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 291307-56-7, Ro 18-5881 291307-57-8, Ro 19-6945

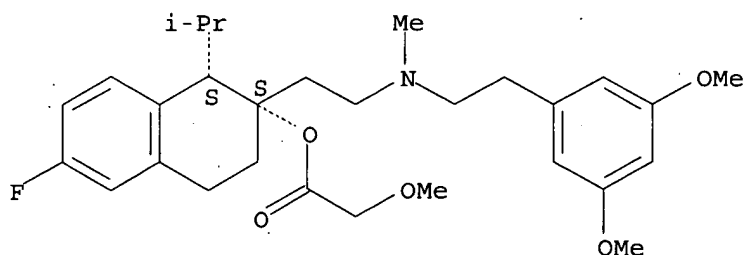
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(high affinity interaction of mibefradil with voltage-gated calcium and sodium channels)

RN 291307-56-7 HCAPLUS

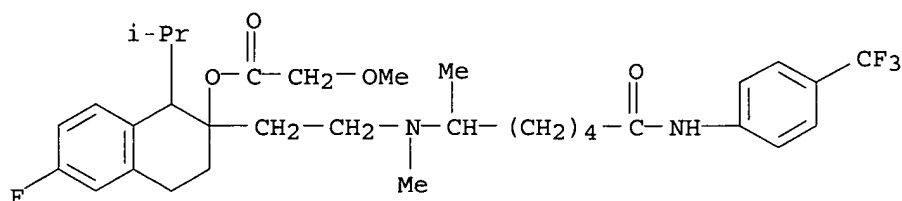
CN Acetic acid, methoxy-, (1S,2S)-2-[2-[2-(3,5-dimethoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 291307-57-8 HCAPLUS

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-[2-[methyl[1-methyl-6-oxo-6-[[4-(trifluoromethyl)phenyl]amino]hexyl]amino]ethyl]-2-naphthalenyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 22 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:840398 HCAPLUS

DOCUMENT NUMBER: 135:40208

TITLE: T-type calcium channel blockade in the management of chronic ischemic heart disease

AUTHOR(S): Marsh, James D.; Antman, Elliott M.

CORPORATE SOURCE: Cardiovascular Division, Department of Internal Medicine, Wayne State University School of Medicine, Detroit, MI, USA

SOURCE: Cardiovascular Drugs and Therapy (2000), 14(5), 459-461

CODEN: CDTHET; ISSN: 0920-3206

PUBLISHER: Kluwer Academic Publishers

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 01 Dec 2000

AB A review with 4 refs. The T-type calcium channel offers a new therapeutic target for treatment of patients with cardiovascular disease. Mibefradil, a T channel blocker, produces heart rate slowing and coronary vasodilatation but without the neg. inotropic effect commonly seen when L-type channel blockers are used. The present study shows Mibefradil prevents ischemic episodes that are and are not preceded by an increase in heart rate. Although Mibefradil has been withdrawn because of multiple drug interactions, new T-type calcium channel blockers are under development.

CC 1-0 (Pharmacology)

IT 116644-53-2, Mibefradil

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(T-type calcium channel blockade in management of chronic ischemic heart disease in humans)

IT 116644-53-2, Mibefradil

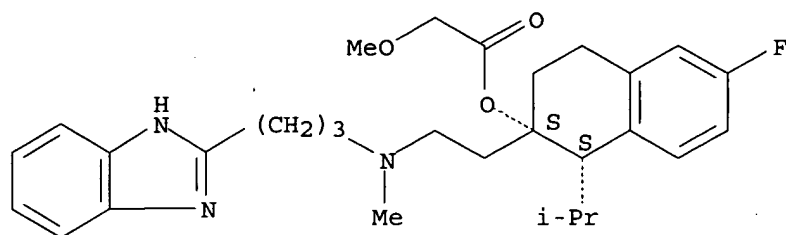
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(T-type calcium channel blockade in management of chronic ischemic heart disease in humans)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 23 OF 198 HCAPLUS' COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:110790 HCAPLUS

DOCUMENT NUMBER: 132:274600

TITLE: N-type calcium channels control sympathetic neurotransmission in human heart atrium

AUTHOR(S): Molderings, G. J.; Likungu, J.; Gothert, M.

CORPORATE SOURCE: The Institute of Pharmacology and Toxicology, University of Bonn, Bonn, D-53113, Germany

SOURCE: Circulation (2000), 101(4), 403-407

CODEN: CIRCAZ; ISSN: 0009-7322

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 16 Feb 2000

AB Because knowledge about the type of calcium channels involved in action potential-induced norepinephrine release from the human peripheral sympathetic nervous system is sparse, the authors investigated which types of calcium channels are functionally important in the sympathetic nerves of human cardiac tissue. In superfused segments of human right atrial appendages, the type of calcium channels that control [3H]norepinephrine release evoked by transmural elec. stimulation was determined [3H]norepinephrine release was almost abolished by 0.2  $\mu$ M  $\omega$ -conotoxin GVIA (a selective blocker of N-type channels) but was not modified by 0.1  $\mu$ M  $\omega$ -agatoxin IVA (a selective blocker of P- and Q-type channels). Mibefradil (a T-type and N-type calcium channel blocker) at concns. of 0.3 to 3  $\mu$ M reduced the evoked tritium overflow in a frequency- and calcium-dependent manner, whereas 0.1 to 10  $\mu$ M amlodipine, diltiazem, and verapamil (selective blockers of L-type channels) were ineffective. Norepinephrine release from cardiac sympathetic nerves is triggered by  $\text{Ca}^{2+}$  influx via N-type but not L- and P/Q-type calcium channels. The inhibitory effect of mibefradil on norepinephrine release at clin. relevant concns. is probably due to its blocking action on N-type  $\text{Ca}^{2+}$  channels. This property of mibefradil is unique among the calcium channel blockers that have been or still are therapeutically applied and may considerably contribute to its slight neg. chronotropic effect in vivo.

CC 2-8 (Mammalian Hormones)

Section cross-reference(s): 1

IT 116644-53-2, Mibefradil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(N-type calcium channels control sympathetic neurotransmission in human heart atrium)

IT 116644-53-2, Mibefradil

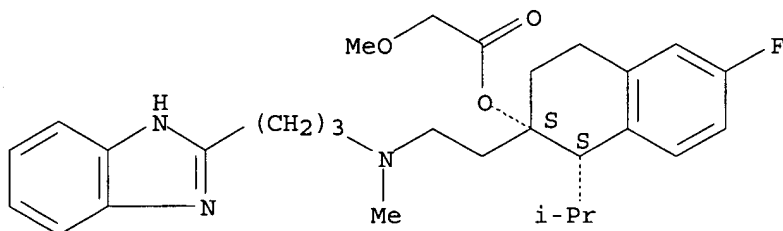
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(N-type **calcium channels** control sympathetic neurotransmission in human **heart** atrium)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 24 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:795648 HCAPLUS

DOCUMENT NUMBER: 132:35723

TITLE: Multibinding, multimeric ligands comprising calcium channel blockers

INVENTOR(S): Ji, Yu-Hau; Natarajan, Maya; Griffin, John H.

PATENT ASSIGNEE(S): Advanced Medicine, Inc., USA

SOURCE: PCT Int. Appl., 166 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 31

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9963992	A1	19991216	WO 1999-US12672	19990607 <--
WO 9963992	C2	20020822		
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CA 2319153	AA	19991216	CA 1999-2319153	19990607 <--
WO 9963984	A1	19991216	WO 1999-US11801	19990607 <--
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 WO 9963932 A2 19991216 WO 1999-US12724 19990607 <--  
 WO 9963932 A3 20000203  
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 AU 9945493 A1 19991230 AU 1999-45493 19990607 <--  
 AU 9945511 A1 19991230 AU 1999-45511 19990607 <--  
 AU 9946726 A 19991230 AU 1999-46726 19990607 <--  
 AU 9946726 A1 19991230  
 EP 1085863 A1 20010328 EP 1999-928427 19990607 <--  
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE  
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 EP 1085879 A2 20010328 EP 1999-928442 19990607 <--  
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 EP 1085890 A1 20010328 EP 1999-930122 19990607 <--  
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 EP 1089749 A1 20010411 EP 1999-928447 19990607 <--  
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 JP 2002517437 T2 20020618 JP 2000-553053 19990607 <--  
 JP 2002517440 T2 20020618 JP 2000-553061 19990607 <--  
 SG 80038 A1 20010417 SG 1999-2716 19990608 <--  
 ZA 2000004562 A 20011130 ZA 2000-4562 20000831 <--  
 ZA 2000004563 A 20011130 ZA 2000-4563 20000831 <--  
 ZA 2000004564 A 20011130 ZA 2000-4564 20000831 <--  
 US 2003044845 A1 20030306 US 2002-75017 20020213 <--  
 US 1998-88465P P 19980608 <--  
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 WO 1999-US12672 W 19990607 <--  
 WO 1999-US12724 W 19990607 <--  
 WO 1999-US12754 W 19990607 <--  
 US 2000-499176 B1 20000207 <--

## PRIORITY APPLN. INFO.:

ED Entered STN: 17 Dec 1999

AB Novel multibinding compds., which are multimeric ligands, are disclosed.  
 The compds. comprise 2-10 ligands, covalently connected via 1-20 linkers,  
 with each ligand being capable of binding to a ligand-binding site in a

Ca++ channel. The ligands may be selected from representative calcium channel blockers, including verapamil, diltiazem, benziazem, clentiazem, nicardipine, nifedipine, nilvadipine, nitrendipine, nimodipine, isradipine, lacidipine, amlodipine, nisoldipine, felodipine, bepridil, mibefradil, SQ 32910, and SQ 32428. The ligands may be identified via a combinatorial library based upon varying ligands and/or linkers. Several prophetic examples are given, using amlodipine, verapamil, diltiazem, and other ligand components.

IC A61K031-33; A61K038-00; A61K039-00; A61K039-44; A61K039-395; A61K051-00; C07K002-00; C07K004-00; G01N033-53; G01N033-543; G01N033-566

CC 28-22 (Heterocyclic Compounds (More Than One Hetero Atom))  
Section cross-reference(s): 1, 27, 63

IT 52-53-9DP, Verapamil, dimeric and multimeric derivs. 21829-25-4DP, Nifedipine, dimeric and multimeric derivs. 39562-70-4DP, Nitrendipine, dimeric and multimeric derivs. 42399-41-7DP, Diltiazem, dimeric and multimeric derivs. 55985-32-5DP, Nicardipine, dimeric and multimeric derivs. 63675-72-9DP, Nisoldipine, dimeric and multimeric derivs. 64706-54-3DP, Bepridil, dimeric and multimeric derivs. 66085-59-4DP, Nimodipine, dimeric and multimeric derivs. 72509-76-3DP, Felodipine, dimeric and multimeric derivs. 75530-68-6DP, Nilvadipine, dimeric and multimeric derivs. 75695-93-1DP, Isradipine, dimeric and multimeric derivs. 88150-42-9DP, Amlodipine, dimeric and multimeric derivs. 96125-53-0DP, Clentiazem, dimeric and multimeric derivs. 103890-78-4DP, Lacidipine, dimeric and multimeric derivs. **116644-53-2DP**, Mibefradil, dimeric and multimeric derivs. 138335-21-4DP, SQ 32910, dimeric and multimeric derivs. 149759-25-1DP, SQ 32428, dimeric and multimeric derivs. 181368-31-0DP, Benziazem, dimeric and multimeric derivs.

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of multibinding multimeric ligands comprising **calcium channel blockers**)

IT **116644-53-2DP**, Mibefradil, dimeric and multimeric derivs.

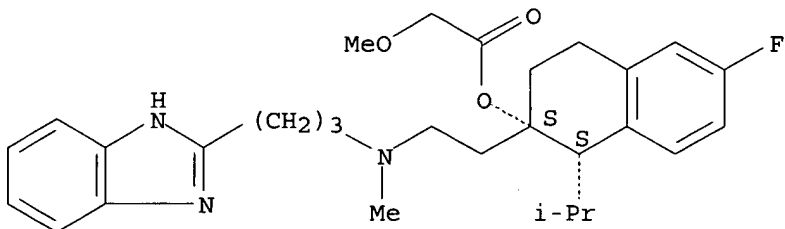
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of multibinding multimeric ligands comprising **calcium channel blockers**)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

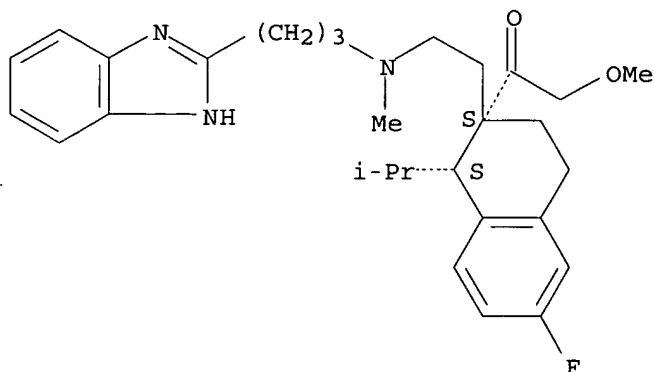
L103 ANSWER 25 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN



ACCESSION NUMBER: 1999:104627 HCAPLUS  
 DOCUMENT NUMBER: 130:205140  
 TITLE: Potential-dependent, T-type calcium channel inhibitors  
 for treatment or prevention of pollakiuria or urinary  
 incontinence  
 INVENTOR(S): Narita, Kazuhisa; Koga, Ichiro; Okada, Atsushi  
 PATENT ASSIGNEE(S): Nippon Kayaku Co., Ltd., Japan  
 SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.  
 CODEN: JKXXAF  
 DOCUMENT TYPE: Patent  
 LANGUAGE: Japanese  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 11035483	A2	19990209	JP 1998-128463	19980512 <--
PRIORITY APPLN. INFO.:			JP 1997-144503	A 19970520 <--
ED Entered STN: 16 Feb 1999				
AB Potential-dependent, T-type calcium channel inhibitors e.g. [1S, 2S]-2-[2-[[3-[2-benzimidazolyl]propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthylmethoxyacetate and 7-[4-[4,4'-difluorobenzohydryl]piperadino-1-methyl]-2-[[2-hydroxyethyl]amino]-4-isopropyl-2,4,6-cycloheptatrien-1-one for treatment or prevention of pollakiuria or urinary incontinence are claimed.				
IC ICM A61K045-00				
ICS A61K031-415; A61K031-445; A61K031-495; C07D235-14; C07D295-12				
CC 1-11 (Pharmacology)				
IT 57-41-0, Phenytoin 1841-19-6, Fluspirilene 26864-56-2, Penfluridol 30484-77-6, Flunarizine hydrochloride 52468-60-7, Flunarizine 220873-01-8 220873-02-9				
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)				
(potential-dependent, T-type calcium channel inhibitors for treatment or prevention of pollakiuria or urinary incontinence)				
IT 220873-01-8				
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)				
(potential-dependent, T-type calcium channel inhibitors for treatment or prevention of pollakiuria or urinary incontinence)				
RN 220873-01-8 HCAPLUS				
CN Ethanone, 1-[(1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl]-2-methoxy- (9CI) (CA INDEX NAME)				

Absolute stereochemistry.



L103 ANSWER 26 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:96707 HCAPLUS

DOCUMENT NUMBER: 133:12548

TITLE: Cardioprotective efficacy of verapamil and mibefradil in young UM-X7.1 cardiomyopathic hamsters

AUTHOR(S): Paquette, France; Jasmin, Gaetan; Dumont, Louis

CORPORATE SOURCE: Departements de Pharmacologie et de Pathologie, Universite de Montreal, Montreal, QC, H3C 3J7, Can.

SOURCE: Cardiovascular Drugs and Therapy (1999), 13(6), 525-530

CODEN: CDTHET; ISSN: 0920-3206

PUBLISHER: Kluwer Academic Publishers

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 11 Feb 2000

AB Since calcium overload and increased in T-type calcium channel activity have been observed in the cardiomyopathic (CM) hamster, we hypothesized that mibefradil (Ro 40-5967), a new T- and L-type calcium channel blocker, may exert significant cardioprotection in the early phase of the disease. Young (30-day-old) CM hamsters of the UM-X7.1 subline were treated with mibefradil or verapamil for 4 to 6 wk. Mibefradil doses were in the range of 0.5 to 8 mg/kg/day while verapamil was given at a dose of 5-10 mg/kg/day, both drugs being injected twice daily (s.c. and i.p. alternatively). At the end of the treatment period, myocardial and skeletal muscle (tongue) were harvested and processed for assessment of necrotic changes and calcification. In hearts from control CM hamsters, numerous necrotic and calcified foci were observed. These myocardial necrosis markers were not attenuated by mibefradil in the dose range studied whereas verapamil significantly reduced their severity. The dystrophic process in skeletal muscle (tongue) was not inhibited by mibefradil or verapamil. These results suggest that mechanisms other than inhibition of T- and L-type calcium channels are related to the cardioprotection observed in the presence of verapamil. A specific action on the sarcoplasmic reticulum (ryanodine-sensitive calcium channel) or the mitochondria may explain the efficacy of phenylalkylamines (verapamil) in this condition.

CC 1-8 (Pharmacology)

IT 116644-53-2, Mibefradil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(cardioprotective efficacy of verapamil and mibefradil in young UM-X7.1 cardiomyopathic hamsters and role of calcium channels)

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(cardioprotective efficacy of verapamil and mibefradil in young UM-X7.1 cardiomyopathic hamsters and role of calcium channels)

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Chemical structure of compound 10: A benzimidazole ring system connected via a  $(\text{CH}_2)_3$  chain to a nitrogen atom. This nitrogen is also bonded to a methyl group and a 4-(4-fluorophenyl)-2-methoxy-1,2,3,4-tetrahydro-1H-benzothiazol-5-yl group. The benzothiazole ring has a methoxycarbonyl group at position 2, an isopropyl group at position 4, and a fluorine atom at position 6.

AB The combination of calcium channel blockers and  $\beta$ -adrenoceptor blockers is more effective for the treatment of exercise-induced angina pectoris than  $\beta$ -adrenoceptor blocker monotherapy. As ischemia in exercise-induced angina is preceded by increase in heart rate, calcium channel blockers with neg. chronotropic properties may perform better for this purpose than nonchronotropic compds. A 335 patient double-blind parallel-group study comparing 14 day treatment with amlodipine 5 and 10 mg, with diltiazem 200 and 300 mg, and mibefradil 50 and 100 mg added to baseline  $\beta$ -adrenoceptor blocker treatment was performed. Exercise testing (ETT) was performed by bicycle ergometry. Although none of the calcium channel blockers improved duration of exercise or amount of workload, all significantly delayed onset of 1 mm ST-segment depression on ETT ( $P < 0.001$  for any treatment vs. baseline). In addition, mibefradil, both low and high dose treatment, produced the longest delays (low dose:

different from diltiazem and amlodipine by 24.1 and 29.8 s, resp.,  $P < 0.003$  and  $< 0.001$ ; high dose: different from diltiazem and amlodipine by 33.7 and 37.0 s, resp.,  $P < 0.001$  and  $< 0.001$ ). These effects were linearly correlated with the reduction in rate pressure product (RPP). Serious symptoms of dizziness occurred significantly more frequently on mibefradil ( $P < 0.05$ ), and 19 patients on mibefradil withdrew from trial. Calcium channel blockers with neg. chronotropic properties provide greater delay of ischemia in patients with exercise-induced angina, but the concomitant risk of intolerable dizziness attenuates this benefit.

CC 1-8 (Pharmacology)

IT **116644-53-2**, Mibefradil

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(combination of **calcium channel** blockers and  $\beta$ -adrenoceptor blockers for treatment of exercise-induced **angina pectoris** in humans)

IT **116644-53-2**, Mibefradil

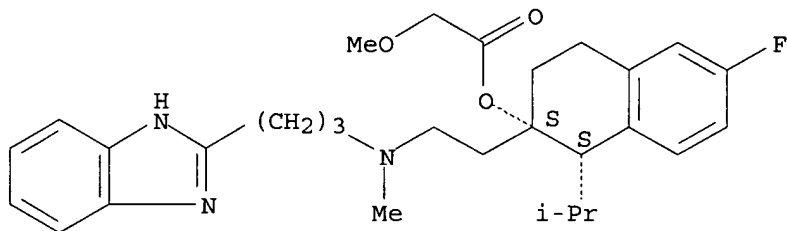
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(combination of **calcium channel** blockers and  $\beta$ -adrenoceptor blockers for treatment of exercise-induced **angina pectoris** in humans)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 28 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:39386 HCAPLUS

DOCUMENT NUMBER: 132:73100

TITLE: L- and T-type calcium channel blockade - the efficacy of the calcium channel antagonist mibefradil

AUTHOR(S): Sandmann, St.; Unger, Th.

CORPORATE SOURCE: Institute of Pharmacology, Christian-Albrechts-University of Kiel, Kiel, D-24105, Germany

SOURCE: Journal of Clinical and Basic Cardiology (1999), 2(2), 187-201

CODEN: JCBCFT; ISSN: 1561-2775

PUBLISHER: Krause & Pachernegg GmbH

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 18 Jan 2000

AB A review with 118 refs. The presence of different subtypes of

voltage-dependent calcium channels was recognized about a decade ago. In heart, neurons, vascular smooth muscle and in endocrine cells, so called L-type and T-type currents coexist. These two types of currents are easily discriminated, especially at the single channel level: channel activity in a test pulse is either long-lived (L-type) or transient (T-type). The currently available calcium channel antagonists (CCA) interact predominantly or exclusively with the L-type calcium channel. However, most of the CCA used in the therapy of hypertension and angina pectoris feature to some extent unwanted effects such as neg. inotropism, atrioventricular blockade or neurohormonal activation. Mibefradil is a CCA that structurally belongs to a new class of benzimidazolyl tetraline derivs. featuring an inhibition of both L- and T-type calcium channels, with a higher selectivity for T-channels. The compound is a potent antihypertensive and antianginal drug with preferential coronary vasodilative effects, without adverse neg. inotropic or pos. chronotropic cardiac actions. Thus, mibefradil offers a new concept in calcium channel antagonism, and can be regarded as a pharmacol. important new development within the group of CCA.

CC 1-0 (Pharmacology)

IT 116644-53-2, Mibefradil

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(potential of new T-type **calcium channel** blocker  
mibefradil in treatment of human **cardiovascular** disease)

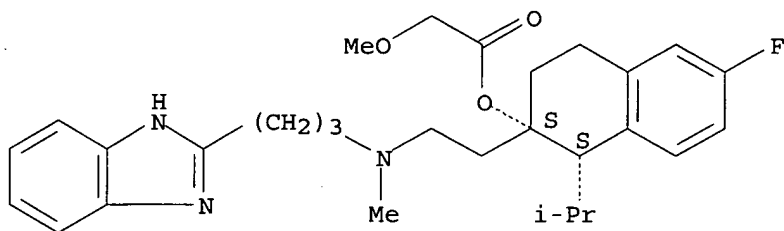
IT 116644-53-2, Mibefradil

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(potential of new T-type **calcium channel** blocker  
mibefradil in treatment of human **cardiovascular** disease)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 118 THERE ARE 118 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 29 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:608109 HCAPLUS

DOCUMENT NUMBER: 132:8827

TITLE: Effects of the calcium channel antagonist mibefradil on hemodynamic parameters and myocardial Ca<sup>2+</sup>-handling in infarct-induced heart failure in rats

AUTHOR(S): Sandmann, S.; Min, J.-Y.; Meissner, A.; Unger, T.

CORPORATE SOURCE: Institute of Pharmacology, Christian-Albrechts-

SOURCE: University of Kiel, Kiel, Germany  
Cardiovascular Research (1999), 44(1), 67-80  
CODEN: CVREAU; ISSN: 0008-6363  
PUBLISHER: Elsevier Science B.V.  
DOCUMENT TYPE: Journal  
LANGUAGE: English

ED Entered STN: 26 Sep 1999

AB Objective: Abnormal intracellular  $\text{Ca}^{2+}$ -handling has been implicated in the pathogenesis of contractile dysfunction and arrhythmias in failing hearts. Calcium channel antagonists (CCA) have been proposed for the prevention of cardiac events after myocardial infarction (MI). Recent studies suggest that the blockade of T-type  $\text{Ca}^{2+}$ -channels induced a heart rate reduction without neg. inotropic effects. We investigated the effects of the preferentially T-channel blocking CCA, mibefradil, on hemodynamic parameters and intramyocardial  $\text{Ca}^{2+}$ -handling and contractility in the early and late period after MI. Methods: MI was induced by permanent ligation of the left coronary artery in male normotensive Wistar rats. Animals were divided in sham-operated and placebo- or mibefradil-treated MI rats. Placebo or Mibefradil treatment (10 mg/kg/d via gastric gavage) was started 7 days prior to MI-induction. Hemodynamic and intramyocardial  $\text{Ca}^{2+}$  measurements were performed 1, 3, 7 and 42 days after surgery. At these time points, mean arterial blood pressure (MAP), heart rate (HR), left ventricular end-diastolic pressure (LVEDP) and cardiac contractility ( $\text{dP/dt}_{\text{max}}$ ) were measured in conscious rats. After hemodynamic measurements, the left ventricular papillary muscle was separated to determine developed tension (DT), time to peak tension (TPT) and systolic and diastolic free intracellular  $\text{Ca}^{2+}$  concns. ( $[\text{Ca}^{2+}]_i$ ) using the  $\text{Ca}^{2+}$  indicator aequorin. Dose-response curves after extracellular isoproterenol- or  $\text{Ca}^{2+}$ -stimulation were recorded. Results: In the early (1-3 days) period after MI, MAP and  $\text{dP/dt}_{\text{max}}$  were decreased and LVEDP and HR were increased in placebo-treated MI rats. Mibefradil treatment increased MAP and  $\text{dP/dt}_{\text{max}}$  and decreased LVEDP and HR in infarcted rats. In the papillary muscle of placebo-treated rats, MI induced a decrease in DT and an increase in TPT and in diastolic and systolic  $[\text{Ca}^{2+}]_i$ . DT of placebo-treated MI rats showed a reduced reactivity after isoproterenol- or  $\text{Ca}^{2+}$ -stimulation. After mibefradil treatment DT was increased and TPT was reduced in the late period (7-42 days) after MI, and diastolic and systolic  $[\text{Ca}^{2+}]_i$  were decreased in the early period after MI (1-3 days). The inotropic response to  $\beta$ -adrenergic or extracellular  $\text{Ca}^{2+}$ -stimulation was markedly improved by mibefradil 7 and 42 days after MI. Conclusion: We conclude, that mibefradil improves cardiac function, protects the myocardium against ischemia-induced  $\text{Ca}^{2+}$ -overload and increases  $\beta$ -adrenergic responsiveness in chronically failing rat hearts.

CC 1-8 (Pharmacology)

IT 116644-53-2, Mibefradil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(effects of **calcium channel** antagonist mibefradil on hemodynamic parameters and myocardial  $\text{Ca}^{2+}$ -handling in infarct-induced **heart** failure in rats)

IT 116644-53-2, Mibefradil

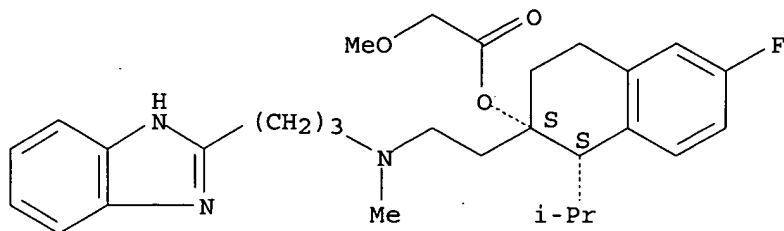
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(effects of **calcium channel** antagonist mibefradil on hemodynamic parameters and myocardial  $\text{Ca}^{2+}$ -handling in infarct-induced **heart** failure in rats)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 30 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:558998 HCAPLUS

DOCUMENT NUMBER: 129:144734

TITLE: Effect of the novel T-selective calcium channel antagonist mibefradil on kidney function in comparison with amlodipine

AUTHOR(S): Greven, Joachim

CORPORATE SOURCE: Department Pharmacology Toxicology, Rheinisch-Westfaelische Technische Hochschule, Aachen, D-52057, Germany

SOURCE: Arzneimittel-Forschung (1998), 48(8), 806-810

CODEN: ARZNAD; ISSN: 0004-4172

PUBLISHER: Editio Cantor Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 02 Sep 1998

AB In the present study, the renal effects of mibefradil (CAS 116666-63-8), a novel calcium channel antagonist which more selectively blocks T-type than L-type calcium channels, was tested by applying clearance techniques to anesthetized rats. The effects of mibefradil on kidney function and on arterial blood pressure were compared with those of the long acting dihydropyridine-type calcium antagonist amlodipine (CAS 88150-42-9). The results show that, within a dosage range of 0.1 to 1.0 mg/kg i.v., mibefradil induced a dose-dependent decrease of arterial blood pressure. Kidney function was not significantly affected at a dose of 0.1 mg/kg. By increasing the dose to 0.3 mg/kg, mibefradil induced a significant increase in urine flow, renal sodium, chloride and potassium excretion. Also fractional sodium and chloride excretions were significantly enhanced at this dose. The diuretic and saluretic effects of mibefradil were accompanied by a significant increase in the glomerular filtration rate. At the highest dose of 1 mg/kg used, the blood pressure lowering effect of mibefradil was most pronounced and glomerular filtration rate rose only slightly and not significantly. At this dose, the enhancement of urine flow and urinary electrolyte excretion was smaller than at the dose of 0.3 mg/kg. The actions of mibefradil were qual. similar to those of the dihydropyridine derivate amlodipine which at a dose of 0.3 mg/kg produced nearly identical renal effects to mibefradil, but exerted stronger antihypertensive effects. This study demonstrates that mibefradil shares with amlodipine the property to

induce, at appropriate doses, diuretic and saluretic effects with a concomitant increase in glomerular filtration rate.

CC 1-8 (Pharmacology)

IT 88150-42-9, Amlodipine **116644-53-2**, Mibefradil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(effect of the novel T-selective **calcium channel**

antagonist mibefradil on kidney function in comparison with amlodipine)

IT **116644-53-2**, Mibefradil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

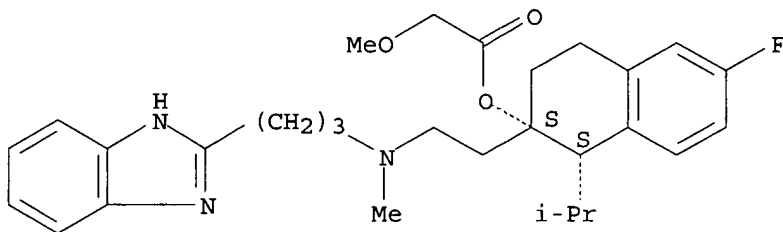
(effect of the novel T-selective **calcium channel**

antagonist mibefradil on kidney function in comparison with amlodipine)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 31 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:681063 HCAPLUS

DOCUMENT NUMBER: 130:47292

TITLE: HERG and KvLQT1/IsK, the cardiac K<sup>+</sup> channels involved in long QT syndromes, are targets for calcium channel blockers

AUTHOR(S): Chouabe, Christophe; Drici, Milou-Daniel; Romey, Georges; Barhanin, Jacques; Lazdunski, Michel

CORPORATE SOURCE: Institut de Pharmacologie Moléculaire et Cellulaire, Centre National de la Recherche Scientifique, Valbonne, F-06560, Fr.

SOURCE: Molecular Pharmacology (1998), 54(4), 695-703

CODEN: MOPMA3; ISSN: 0026-895X

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 28 Oct 1998

AB We examined the effects of the calcium channel blockers nitrendipine, diltiazem, verapamil, bepridil, and mibefradil on the cloned HERG and KvLQT1/IsK K<sup>+</sup> channels. These channels generate the rapid and slow components of the cardiac delayed rectifier K<sup>+</sup> current, and mutations can affect them, which leads to long QT syndromes. When expressed in transfected COS cells, HERG is blocked in a concentration-dependent manner by bepridil (EC<sub>50</sub> = 0.55 μM), verapamil (EC<sub>50</sub> = 0.83 μM), and mibefradil (EC<sub>50</sub> = 1.43 μM), whereas nitrendipine and diltiazem have negligible effects. Steady state activation and inactivation parameters



are shifted to more neg. values in the presence of the blockers. Similarly, KvLQT1/IsK is inhibited by bepridil (EC50 = 10.0  $\mu$ M) and mibefradil (EC50 = 11.8  $\mu$ M), while being insensitive to nitrendipine, diltiazem, or verapamil. These results demonstrate that both cloned K<sup>+</sup> channels HERG and KvLQT1/IsK, which represent together the cardiac delayed rectifier K<sup>+</sup> current, are sensitive targets to calcium channel blockers. This work may help in understanding the mechanisms of action of verapamil in certain ventricular tachycardia, as well as some of the deleterious adverse cardiac events associated with bepridil.

CC 1-8 (Pharmacology)

IT 52-53-9, Verapamil 39562-70-4, Nitrendipine 42399-41-7, Diltiazem 116644-53-2, Mibefradil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(HERG and KvLQT1/IsK, the **cardiac** K<sup>+</sup> channels involved in long QT syndromes, are targets for **calcium channel blockers**)

IT 116644-53-2, Mibefradil

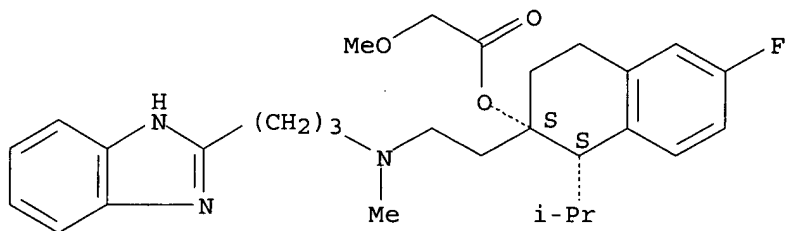
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(HERG and KvLQT1/IsK, the **cardiac** K<sup>+</sup> channels involved in long QT syndromes, are targets for **calcium channel blockers**)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 32 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:513374 HCAPLUS

DOCUMENT NUMBER: 129:225509

TITLE: Effects of the calcium channel antagonist mibefradil on hemodynamic and morphological parameters in myocardial infarction-induced cardiac failure in rats

AUTHOR(S): Sandmann, Steffen; Spitznagel, Heidi; Chung, Oliver; Xia, Qin-Gui; Illner, Sascha; Janichen, Gunnar; Rossius, Birthe; Daemen, Mat J. A. P.; Unger, Thomas

CORPORATE SOURCE: Institute of Pharmacology, Christian-Albrechts-University of Kiel, Kiel, 24105, Germany

SOURCE: Cardiovascular Research (1998), 39(2), 339-350

CODEN: CVREAU; ISSN: 0008-6363

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 19 Aug 1998

AB Calcium channel antagonists (CCA) have been proposed for the prevention of cardiac events after myocardial infarction (MI). Mibefradil is a CCA featuring a selective blockade of T-type  $\text{Ca}^{2+}$ -channels. The aim of the study was to characterize the effects of mibefradil on hemodynamic and morphol. parameters in a model of postMI chronic heart failure and to establish the "therapeutic window" for the start of therapy. MI was induced by permanent ligation of the left coronary artery in male normotensive Wistar rats. Animals were assigned to placebo- or mibefradil-treated (10 mg/kg/day p.o.) groups as follows: (1) sham operation; (2) MI placebo treatment; (3) 7 days preMI start of treatment; (4) 3 h postMI start of treatment; (5) 24 h postMI start of treatment; (6) 3 days postMI start of treatment; (7) 7 days postMI start of treatment. Treatment was continued for 6 wk postMI. At this time point, mean arterial blood pressure (MAP), heart rate, left ventricular end diastolic pressure (LVEDP) and contraction force (dP/dtmax) were measured in conscious rats at baseline and after methoxamine (MEX; 0.5-1.0 mg/h i.v.) stimulation to increase afterload. The hearts were subjected to histol. determination of infarct size (IS), infarct length (IL), noninfarcted length

(NL), left ventricular circumference (LVC), inner LV-diameter (LVD) and septal thickness (ST). Six weeks after MI, MAP was lowered, LVEDP increased and dP/dtmax reduced. Mibefradil treatment increased basal MAP in groups 3-5 compared to the placebo-treated MI group. Under mibefradil, LVEDP was reduced at baseline in groups 3-6 and, after MEX, in all groups. dP/dtmax was increased in groups 3-4 at baseline and after MEX. In the placebo-treated MI group, the infarcted area was 39% of the LV and heart weight, LVD and LVC were increased. Heart wts. of mibefradil-treated rats (groups 3-6) did not differ from those of the placebo-treated group. Early onset of treatment with mibefradil reduced IS and IL and increased NL in groups 3-4. LVD and LVC were decreased in group 3 only. ST was increased in groups 3-5. Chronic treatment with mibefradil exerts beneficial actions on cardiac structure and performance in postMI cardiac failure in rats, especially when the onset of treatment is either prior to or within hours after the acute ischemic event.

CC 1-8 (Pharmacology)

IT 116644-53-2, Mibefradil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(calcium channel antagonist mibefradil effect on hemodynamic and morphol. parameters in myocardial infarction-induced cardiac failure)

IT 116644-53-2, Mibefradil

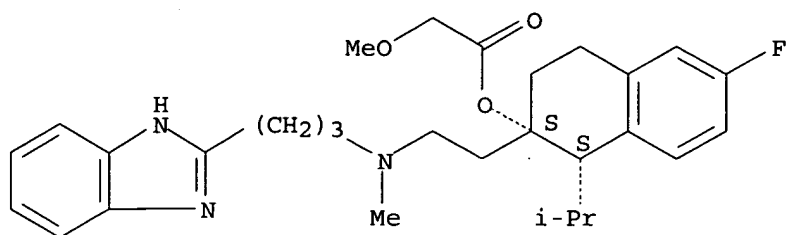
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(calcium channel antagonist mibefradil effect on hemodynamic and morphol. parameters in myocardial infarction-induced cardiac failure)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 33 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:634577 HCAPLUS

DOCUMENT NUMBER: 129:325922

TITLE: Human vascular to cardiac tissue selectivity of L- and T-type calcium channel antagonists

AUTHOR(S): Sarsero, Doreen; Fujiwara, Toshimasa; Molenaar, Peter; Angus, James A.

CORPORATE SOURCE: Department of Pharmacology, University of Melbourne, Parkville, 3052, Australia

SOURCE: British Journal of Pharmacology (1998), 125(1), 109-119

CODEN: BJPCBM; ISSN: 0007-1188

PUBLISHER: Stockton Press

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 08 Oct 1998

AB Voltage-operated calcium channel (VOCC) antagonists are effective antihypertensive and antianginal agents but they also depress myocardial contractility. We compared four L-type calcium channel antagonists, felodipine, nifedipine, amlodipine and verapamil and a relatively T-type selective calcium channel antagonist, mibefradil, on human and rat isolated tissue assays to determine their functional vascular to cardiac tissue selectivity (V/C) ratio. The V/C ratio was calculated as the ratio of the IC<sub>50</sub> value of the antagonist that reduced (by 50%) submaximally contracted (K<sup>+</sup> 62 mM) human small arteries from the aortic vasa vasorum (vascular, V) mounted in a myograph and the IC<sub>50</sub> value of the antagonist that reduced (-)-isoprenaline (6 nM) submaximally stimulated human right atrial trabeculae muscle (cardiac, C) mounted in organ chambers. The average pIC<sub>50</sub> values (-log IC<sub>50</sub> M) for the human vascular prepns. were felodipine 8.30, nifedipine 7.78, amlodipine 6.64, verapamil 6.26 and mibefradil 6.22. The average pIC<sub>50</sub> values for the cardiac muscle were felodipine 7.21, nifedipine 6.95, verapamil 6.91, amlodipine 5.94, and mibefradil 4.61. The V/C ratio calculated as antilog [pIC<sub>50</sub> V-pIC<sub>50</sub> C] is thus mibefradil 41, felodipine 12, nifedipine 7, amlodipine 5 and verapamil 0.2. In rat small mesenteric arteries the pIC<sub>50</sub> values for the five drugs were similar to the values for human vasa vasorum arteries contracted by K<sup>+</sup> 62 mM. However for methoxamine (10 μM) contraction in the rat arteries the pIC<sub>50</sub> values were lower for felodipine 7.24 and nifedipine 6.23, but similar for verapamil 6.13, amlodipine 6.28 and mibefradil 5.91. In conclusion, in the human tissue assays, the putative T-channel antagonist mibefradil shows the highest vascular to cardiac selectivity ratio; some 3 fold higher than the dihydropyridine, felodipine, and some 200 fold more vascular selective than the phenylalkylamine, verapamil. This favorable vascular to cardiac selectivity for mibefradil, from a new chemical class of VOCC antagonist, may be explained by its putative T-channel selectivity.

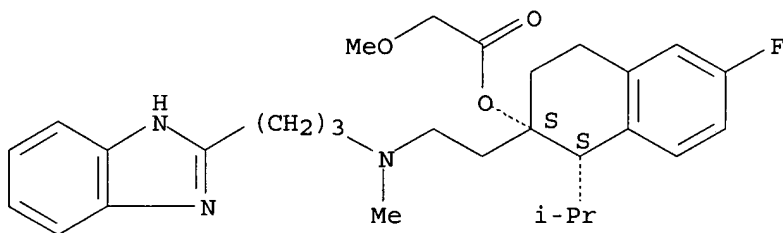
CC 1-8 (Pharmacology)

IT 52-53-9, Verapamil 21829-25-4, Nifedipine 72509-76-3, Felodipine 88150-42-9, Amlodipine **116644-53-2**, Mibefradil  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (vascular to **cardiac** human tissue selectivity of L- and T-type **calcium channel** antagonists)

IT **116644-53-2**, Mibefradil  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (vascular to **cardiac** human tissue selectivity of L- and T-type **calcium channel** antagonists)

RN 116644-53-2 HCAPLUS  
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Absolute stereochemistry.



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 34 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:333486 HCAPLUS

DOCUMENT NUMBER: 129:120419

TITLE: The physiological and pharmacological significance of cardiovascular T-type, voltage-gated calcium channels

AUTHOR(S): Triggle, David J.

CORPORATE SOURCE: State University of New York at Buffalo, Buffalo, NY, 14260, USA

SOURCE: American Journal of Hypertension (1998), 11(4, Pt. 3), 80S-87S

CODEN: AJHYE6; ISSN: 0895-7061

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 04 Jun 1998

AB A review with 44 refs. An influx of calcium ions into cells, made possible by the opening of specific, voltage-gated channels, triggers muscular contraction and several other physiol. processes. Two types of calcium channels, L-type and T-type, are found in the cardiovascular system. These two types of channels differ considerably in their elec. and chemical characteristics and in their distribution in tissue. The L-type calcium channel is responsible for normal myocardial contractility and for vascular smooth muscle contractility. In contrast, T-type calcium channels are not normally present in the adult myocardium, but are prominent in conducting and pacemaking cells. They are thought to help regulate vascular tone, signal conduction, cardiac pacemaking, and the secretion of certain intercellular transmitters. T-Type channels also

seem to have an important role in normal growth processes and in the tissue remodeling that occurs in pathol. processes such as cardiac hypertrophy. Traditional calcium antagonists act on L-type channels. Mibefradil is a recently characterized calcium antagonist and the first that is selective for T-type calcium channels. This unique property may lead to major applications in cardiovascular medicine.

CC 13-0 (Mammalian Biochemistry)

Section cross-reference(s): 1

IT 116644-53-2, Mibefradil

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(physiol. and pharmacol. significance of **cardiovascular**  
T-type, voltage-gated **calcium channels**)

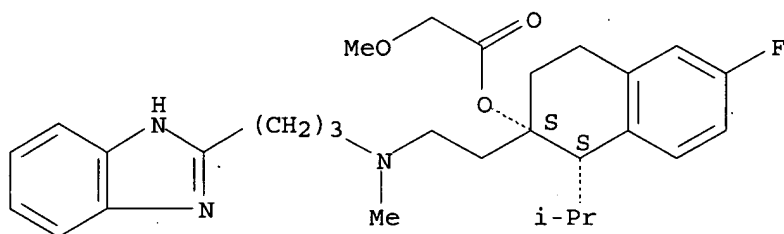
IT 116644-53-2, Mibefradil

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(physiol. and pharmacol. significance of **cardiovascular**  
T-type, voltage-gated **calcium channels**)

RN 116644-53-2 HCAPLUS

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Absolute stereochemistry.



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 35 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:232741 HCAPLUS

DOCUMENT NUMBER: 128:316781

TITLE: Calcium channel blockers in heart failure

AUTHOR(S): Elkayam, Uri

CORPORATE SOURCE: Division of Cardiology, Department of Medicine,  
University of Southern California School of Medicine,  
Los Angeles, CA, 90033, USA

SOURCE: Cardiology (1998), 89(Suppl. 1), 38-46

CODEN: CAGYAO; ISSN: 0008-6312

PUBLISHER: S. Karger AG

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 25 Apr 1998

AB A review with 75 refs. A considerable effort has been made in the last 15 yr to evaluate the safety and efficacy of calcium channel blockers (CCBs) in the treatment of patients with chronic congestive heart failure (CHF). Available studies have provided strong evidence for a potential detrimental effect of the first-generation calcium antagonists in patients with CHF, indicating the need for great caution when these drugs are used in patients with significant depression of left ventricular systolic function. A number of second-generation CCB have demonstrated a strong vasodilatory effect and favorable hemodynamic action but failed to show a similar improvement in exercise capacity, morbidity and mortality.

Moreover, drugs such as nicardipine and nisoldipine have resulted in a detrimental effect in some patients and, therefore, cannot be considered safe when used in patients with moderate-to-severe heart failure. Available information from the V-HeFT III study demonstrate a lack of an unfavorable effect of felodipine on exercise tolerance in patients with chronic heart failure. Although mortality rate was similar in both the felodipine and the placebo group, because of the relatively small number of patients in this study, no clear conclusion can be drawn regarding the effect of felodipine on mortality in patients with CHF. An encouraging signal regarding a potential role of CCB in the treatment of chronic heart failure has been provided by the recently completed PRAISE study. This prospective large-scale study demonstrated the safety of amlodipine, a long-acting dihydropyridine derivative, when used in patients with heart failure due to coronary artery disease. Furthermore, this study demonstrated a substantial reduction in mortality in patients with CHF due to nonischemic cardiomyopathy and provided a strong indication for a potential therapeutic benefit of amlodipine when added to standard CHF therapy in this patient population. No clear explanation is available at the present time regarding the reason for the deleterious effect demonstrated with some of the dihydropyridines and the contrasting benefit seen with amlodipine. Finally, more information regarding the safety and efficacy of dihydropyridines should become available in the next year. The PRAISE II study is ongoing and will provide further information regarding the therapeutic role of amlodipine in patients with nonischemic dilated cardiomyopathy. The MACH-1 study is evaluating the effect of mibefradil, a predominant T-type channel blocker with an ideal activity profile, on morbidity and mortality in patients with chronic CHF.

CC 1-0 (Pharmacology)

IT 52-53-9, Verapamil 42399-41-7, Diltiazem 55985-32-5, Nicardipine 63675-72-9, Nisoldipine 72509-76-3, Felodipine 88150-42-9, Amlodipine 116644-53-2, Mibefradil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(calcium channel blockers in heart failure)

IT 116644-53-2, Mibefradil

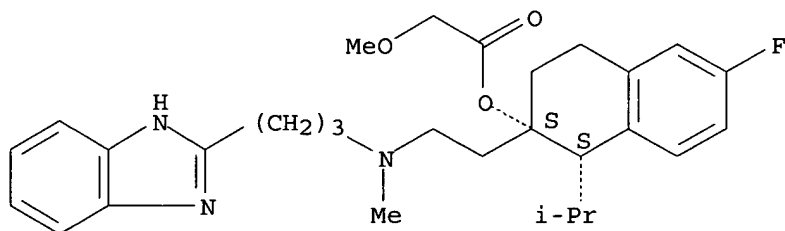
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(calcium channel blockers in heart failure)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS

## RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 36 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:316689 HCAPLUS

DOCUMENT NUMBER: 127:13238

TITLE: Effects of calcium channel antagonists on Ca<sup>2+</sup> transients in rat and canine cardiomyocytes

AUTHOR(S): Hensley, James; Billman, George E.; Johnson, J. David; Hohl, Charlene M.; Altschuld, Ruth A.

CORPORATE SOURCE: Departments of Medical Biochemistry and Physiology, The Ohio State University College of Medicine, Columbus, OH, 43210-1218, USA

SOURCE: Journal of Molecular and Cellular Cardiology (1997), 29(3), 1037-1043

CODEN: JMCDAJ; ISSN: 0022-2828

PUBLISHER: Academic

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 17 May 1997

AB First-generation Ca<sup>2+</sup> channel antagonists depress myocardial contractility, but many of the newer Ca<sup>2+</sup> channel blockers have a high degree of "vascular selectivity". This study compares the effects of the Ca<sup>2+</sup> antagonists felodipine, amlodipine, mibefradil, verapamil and nifedipine, and the Ca<sup>2+</sup> channel agonist, (S)(-)-Bay K-8644 on Ca<sup>2+</sup> transient amplitudes in fura-2/AM-loaded rat and canine ventricular cardiomyocytes. At 10<sup>-11</sup> and 10<sup>-10</sup> M, felodipine increased [Ca<sup>2+</sup>]<sub>i</sub> transient amplitudes by 10-25% in field-stimulated fura-2-loaded cells from both species while at 10<sup>-6</sup> M it depressed [Ca<sup>2+</sup>]<sub>i</sub> transients by 80%. Mibefradil increased [Ca<sup>2+</sup>]<sub>i</sub> transient amplitudes by 16% at 10<sup>-11</sup> and 10<sup>-10</sup> M and decreased the transients by 25% at 10<sup>-6</sup> M. The calcium channel agonist, (S)(-)-Bay K-8644 increased [Ca<sup>2+</sup>]<sub>i</sub> transient amplitudes at 10<sup>-10</sup>-10<sup>-6</sup> M (maximally 37% at 10<sup>-7</sup> M) but depressed [Ca<sup>2+</sup>]<sub>i</sub> transients by 10% at 10<sup>-5</sup> M. Nifedipine was inhibitory at all concns. tested (10<sup>-11</sup>-10<sup>-6</sup> M) in canine myocytes, but in rat cells, 10<sup>-10</sup> M nifedipine increased [Ca<sup>2+</sup>]<sub>i</sub> transient amplitudes by 37%. All concns. of verapamil and amlodipine (10<sup>-11</sup>-10<sup>-6</sup> M) depressed [Ca<sup>2+</sup>]<sub>i</sub> transients in both rat and canine myocytes. We conclude that: (1) felodipine and mibefradil may be pos. rather than neg. inotropes at low concns., which are therapeutically relevant; and (2) low concns. of nifedipine may have a pos. inotropic effect in the rat but not the dog heart.

CC 1-8 (Pharmacology)

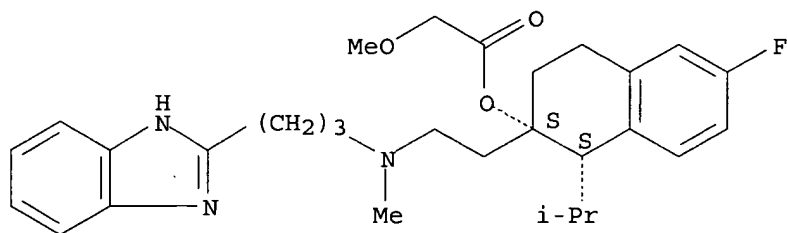
IT 52-53-9, Verapamil 21829-25-4, Nifedipine 72509-76-3, Felodipine 88150-42-9, Amlodipine 116644-53-2, Mibefradil  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
(effects of calcium channel antagonists on Ca<sup>2+</sup> transients in rat and canine cardiomyocytes)

IT 116644-53-2, Mibefradil  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
(effects of calcium channel antagonists on Ca<sup>2+</sup> transients in rat and canine cardiomyocytes)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 37 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:439349 HCAPLUS

DOCUMENT NUMBER: 127:130672

TITLE: Effects of the novel T-type calcium channel antagonist mibefradil on human myocardial contractility in comparison with nifedipine and verapamil

AUTHOR(S): Cremers, Bodo; Flesch, Markus; Suedkamp, Michael; Boehm, Michael

CORPORATE SOURCE: Klinik III fur Innere Medizin der Universitat zu Koln, Koln, 50924, Germany

SOURCE: Journal of Cardiovascular Pharmacology (1997), 29(5), 692-696

CODEN: JCPCDT; ISSN: 0160-2446

PUBLISHER: Lippincott-Raven

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 14 Jul 1997

AB Mibefradil (Ro 40-5967) is a novel nondihydropyridine calcium antagonist. The aim of our study was to compare the neg. inotropic effects of the well-known 1,4-dihydropyridine nifedipine and the phenylalkylamine verapamil with those of mibefradil. Isometric force of contraction in response to these substances was determined in isolated, elec. driven left ventricular papillary muscle strips from failing human hearts (1 Hz, 37°C). The hearts were obtained during cardiac transplantation (n = 9) and mitral valve-replacement operations (n = 9). The calcium antagonists studied significantly (p < 0.05) depressed basal force of contraction in a concentration-dependent manner. The effect started at concns. >0.001 µM for nifedipine and >0.01 µM for verapamil, but only at concns. >10 µM for mibefradil. Only in the presence of nifedipine and verapamil was a significant rightward shift of the inotropic concentration-response curves to calcium and a depression of the maximal effects

of calcium observed With respect to the relation between the therapeutic active plasma concentration in vivo and the neg. inotropic potency in vitro, it became evident that the difference between therapeutically beneficial concns. and potentially hazardous cardiodepressant activity increases from nifedipine to mibefradil. We conclude that this new generation of calcium antagonists, almost lacking cardiodepressant effects, could lead to a greater therapeutic index and greater safety in the treatment of cardiovascular diseases.

CC 1-8 (Pharmacology)

IT 52-53-9, Verapamil 21829-25-4, Nifedipine 116644-53-2, Mibefradil

RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(calcium channel antagonist mibefradil neg.



inotropic and **cardiodepressant** activity in comparison with nifedipine and verapamil)

IT 116644-53-2, Mibefradil

RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

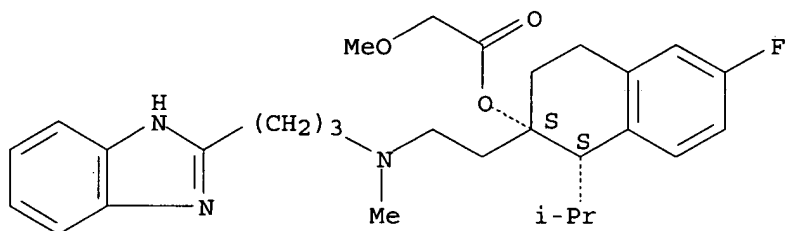
(**calcium channel** antagonist mibefradil neg.

inotropic and **cardiodepressant** activity in comparison with nifedipine and verapamil)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 38 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:150785 HCAPLUS

DOCUMENT NUMBER: 126:181122

TITLE: Increased survival after long-term treatment with mibefradil, a selective T-channel calcium antagonist, in heart failure

AUTHOR(S): Mulder, Paul; Richard, Vincent; Compagnon, Patricia; Henry, Jean-Paul; Lallemand, Francoise; Clozel, Jean-Paul; Koen, Robert; Mace, Bertrand; Thuillez, Christian

CORPORATE SOURCE: Department of Pharmacology, Groupe Vaisseaux, Rouen University Medical School, Rouen, Fr.

SOURCE: Journal of the American College of Cardiology ( 1997), 29(2), 416-421

CODEN: JACCDI; ISSN: 0735-1097

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 07 Mar 1997

AB We sought to investigate the effects of mibefradil on survival, hemodynamic variables and cardiac remodeling in a rat model of chronic heart failure (HF) and to compare these effects with those of the angiotensin-converting enzyme (ACE) inhibitor cilazapril. The use of calcium channel blocking agents in chronic HF has been disappointing. Most studies have shown that these drugs have either no or even detrimental effects due in part to the neg. inotropic effects they induce. Mibefradil is a calcium channel blocker that selectively blocks T channels and displays moderately neg. inotropic properties only at high doses. Because T channels are upregulated in the hypertrophied heart and could mediate hypertrophic signals and increase arrhythmogenicity, blockade of these channels might be beneficial in chronic HF. Rats were subjected to coronary artery ligation and 9 mo of treatment with mibefradil (15 mg/kg body weight per day) or cilazapril (10 mg/kg per day) or no treatment. Survival and systolic blood pressure were assessed over the 9-mo treatment

period, after which cardiac hemodynamic variables and structure were determined. Mibefradil increased survival rate to the same extent as cilazapril (71% for mibefradil vs. 75% for cilazapril and 44% for no treatment). Mibefradil decreased systolic blood pressure, although to a lesser extent than cilazapril. Both treatments decreased left ventricular (LV) end-diastolic and central venous pressures, without any change in the first derivative of LV pressure over time or heart rate. Mibefradil decreased LV weight (although less than cilazapril) without affecting right ventricular weight. Finally, both drugs normalized LV collagen d. Mibefradil in a rat model improved survival to the same extent as an ACE inhibitor, without impairing LV function, and was associated with a reduction in LV weight and fibrosis. Thus, mibefradil might be beneficial in the treatment of chronic HF.

CC 1-8 (Pharmacology)

IT 88768-40-5, Cilazapril **116644-53-2**, Mibefradil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(increased survival after long-term treatment with T-channel calcium antagonist mibefradil in heart failure)

IT **116644-53-2**, Mibefradil

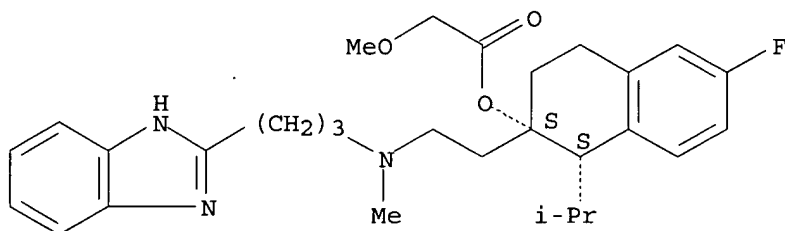
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(increased survival after long-term treatment with T-channel calcium antagonist mibefradil in heart failure)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 39 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:87281 HCAPLUS

DOCUMENT NUMBER: 128:203265

TITLE: Cardiovascular T-type calcium channels: physiological and pharmacological significance

AUTHOR(S): Triggle, David J.

CORPORATE SOURCE: The Graduate School, State University of New York, Buffalo, NY, 14260-1200, USA

SOURCE: Journal of Hypertension (1997), 15(Suppl. 5), S9-S15

CODEN: JOHYD3; ISSN: 0263-6352

PUBLISHER: Rapid Science Publishers

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 14 Feb 1998

AB A review, with 59 refs. A variety of Ca<sup>2+</sup> control processes are

responsible for Ca<sup>2+</sup> homeostasis and signaling. Voltage-gated Ca<sup>2+</sup> channels are dominant in the cardiovascular system. There are several distinct subclasses of Ca<sup>2+</sup> channels, distinguished by location, bio-phys., structural and pharmacol. characteristics. They include both high- and low-voltage-activated channels. The long-lasting (L) type of high-voltage-activated channel is well characterized and is the site of action for the existing clin. available Ca<sup>2+</sup> channel antagonists: nifedipine, verapamil and diltiazem. The low-voltage-activated transient (T-type) channel is widespread in the cardiovascular system and in neurons. It serves pacemaking functions and supports Ca<sup>2+</sup> signaling in secretory cells and vascular smooth muscle. The T-type channel also functions in cell growth processes under physiol. and pathol. conditions. Mibefradil (Ro 40-5967) is a structurally novel Ca<sup>2+</sup> antagonist with selectivity for T-type over L-type channels. This selectivity may underlie its vasodilating activity and heart rate depressive effect, its lack of neg. inotropy and its cardioprotective properties.

CC 13-0 (Mammalian Biochemistry)

Section cross-reference(s): 1

IT 116644-53-2, Mibefradil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(cardiovascular T-type calcium channels  
physiol. and pharmacol. significance)

IT 116644-53-2, Mibefradil

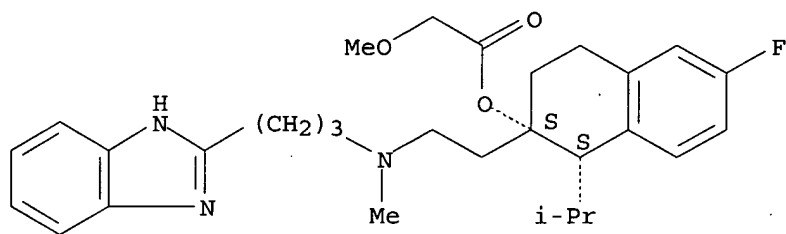
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(cardiovascular T-type calcium channels  
physiol. and pharmacol. significance)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L103 ANSWER 40 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1996:642037 HCAPLUS

DOCUMENT NUMBER: 125:292618

TITLE: Hemodynamic and cardiac effects of the selective T-type and L-type calcium channel blocking agent mibefradil in patients with varying degrees of left ventricular systolic dysfunction

AUTHOR(S): Rousseau, Michel F.; Hayashida, Wataru; Van Eyll, Christian; Hess, Otto M.; Benedict, Claude R.; Ahn, Sylvie; Chapelle, Frederic; Kobrin, Isaac; Pouleur, Hubert

CORPORATE SOURCE: Division Cardiology, University Louvain, Brussels,

SOURCE: B-1200, Belg.  
Journal of the American College of Cardiology (1996), 28(4), 972-979  
CODEN: JACCDI; ISSN: 0735-1097

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 31 Oct 1996

AB This study sought to assess the hemodynamic and cardiac effects of two dose levels of mibefradil in patients with varying degrees of ischemic left ventricular dysfunction. Mibefradil is a new, selective T-type and L-type calcium channel blocking agent. Because L-type channel blockade may depress myocardial performance, an invasive hemodynamic study was performed to assess the safety of this agent. The authors performed an open label study, examining the effects of two i.v. doses of mibefradil, selected to produce plasma levels comparable to those measured after oral administration of 50 mg (dose 1: 400 ng/mL) or 100 mg (dose 2: 800 ng/mL) of the drug. Variables studied included the indexes of left ventricular function and neurohormone levels. Patients were stratified according to ejection fraction (EF) ( $\geq 40\%$ ;  $< 40\%$ ) and the presence or absence of heart failure. In patients with preserved systolic function, dose 1 had no clin. significant hemodynamic effects, but dose 2 decreased mean aortic pressure and systemic vascular resistance ( $-8.5$  mm Hg,  $-12\%$ , both) and also reduced end-systolic stress and volume, thus improving EF ( $52\%$  to  $58\%$ ). Heart rate tended to decrease. In patients with depressed EF, heart rate decreased significantly with both doses. The effects of dose 1 mimicked those observed after dose 2 in patients with preserved EF. Dose 2 (plasma levels  $1052$  ng/mL) still decreased left ventricular systolic wall stress and improved EF ( $24.0\%$  to  $28.5\%$ ) but also significantly depressed the maximal first derivative of left ventricular pressure. Examination of individual pressure-volume loops in two patients with heart failure showed a clear rightward shift of the loop despite a decrease in systolic pressure, suggesting neg. inotropy. Neurohormone levels were unchanged at both dose levels and in all subgroups. I.v. mibefradil was well tolerated and produced an overall favorable cardiovascular response. However, high plasma concns. might produce myocardial depression in patients with heart failure, and caution should be exerted in this setting.

CC 1-8 (Pharmacology)

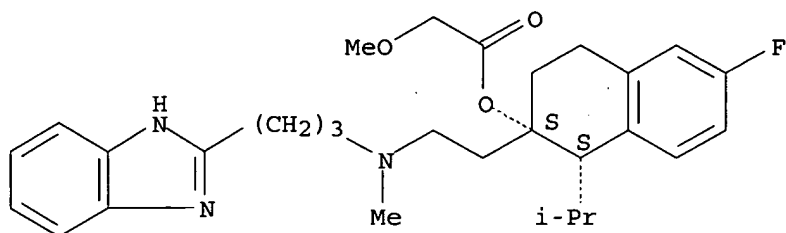
IT 116644-53-2, Mibefradil  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(hemodynamic and **cardiac** effects of selective T-type and L-type **calcium channel** blocking agent mibefradil in human patients with varying degrees of left ventricular systolic dysfunction)

IT 116644-53-2, Mibefradil  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(hemodynamic and **cardiac** effects of selective T-type and L-type **calcium channel** blocking agent mibefradil in human patients with varying degrees of left ventricular systolic dysfunction)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 41 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1996:735832 HCAPLUS

DOCUMENT NUMBER: 126:14196

TITLE: Pharmacologic and therapeutic differences among calcium channel antagonists: Profile of mibefradil, a new calcium antagonist

AUTHOR(S): Triggie, David J.

CORPORATE SOURCE: State University New York, Buffalo, NY, 14260, USA

SOURCE: American Journal of Cardiology (1996), 78(9A), 7-12

CODEN: AJCDAG; ISSN: 0002-9149

PUBLISHER: Excerpta Medica

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 14 Dec 1996

AB A review with 41 refs. Calcium antagonists are a heterogeneous group of drugs, each with a different chemical structure and cardiovascular profile. Distinguishing factors include pharmacokinetics, mode of calcium mobilization affected, class and subclass of calcium channel inhibited, state-dependent interactions, and effect of disease on the drug's activity. A new calcium antagonist, mibefradil, has a unique chemical structure and cardiovascular profile compared with those currently available, and it appears to represent a new class of calcium antagonists.

CC 1-0 (Pharmacology)

IT 116644-53-2, Mibefradil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(pharmacol. and therapeutic differences among calcium channel antagonists and profile of new agent mibefradil as cardiovascular agents in humans and laboratory animals)

IT 116644-53-2, Mibefradil

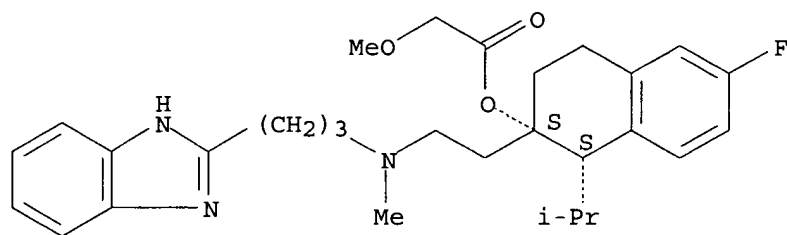
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(pharmacol. and therapeutic differences among calcium channel antagonists and profile of new agent mibefradil as cardiovascular agents in humans and laboratory animals)

RN 116644-53-2 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 42 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:471721 HCAPLUS

DOCUMENT NUMBER: 122:281834

TITLE: Expression of the L-type calcium channel with two different  $\beta$  subunits and its modulation by Ro 40-5967

AUTHOR(S): Welling, Andrea; Lacinova, Lubica; Donatin, Kirsten; Ludwig, Andreas; Bosse, Eva; Flockerzi, Veit; Hofmann, Franz

CORPORATE SOURCE: Inst. Pharmakol. Toxikol., Technische Univ. Muenchen, Munich, D-80802, Germany

SOURCE: Pfluegers Archiv (1995), 429(3), 400-11

CODEN: PFLABK; ISSN: 0031-6768

PUBLISHER: Springer

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 07 Apr 1995

AB The smooth muscle  $\alpha 1\text{C}\beta$  subunit of the L-type calcium channel was expressed alone (CHO $\alpha 1$  cell) or together with the skeletal  $\beta 1$  (CHO $\alpha 1\beta 1$  cell) subunit or smooth muscle  $\beta 3$  (CHO $\alpha 1\beta 3$  cell) subunit in Chinese hamster ovary (CHO) cells. The interaction of the expressed calcium channels with the non-dihydropyridine calcium channel blocker Ro 40-5967 was studied. Ro 40-5967 decreased isradipine binding by an apparent allosteric interaction and blocked the barium inward currents (IBa) in a voltage- and use-dependent manner in all cells. The steady-state inactivation curves were shifted to hyperpolarizing potentials in the presence of Ro 40-5967. The rate of channel inactivation was increased in CHO $\alpha 1$  and CHO $\alpha 1\beta 3$  cells. The shift in the steady-state inactivation curve and the increase in channel inactivation were less pronounced in CHO $\alpha 1\beta 1$  cells than in the other cell lines. Low concns. of Ro 40-5967 increased IBa by up to 198% in 33% of the CHO $\alpha 1\beta 1$  cells. In addition, higher concns. of Ro 40-5967 were required to inhibit IBa in 60% of the CHO $\alpha 1\beta 3$  cells. These results suggest that the  $\beta$  subunits modify the interaction of the non-dihydropyridine Ro 40-5967 with the expressed calcium channel  $\alpha 1$  subunit.

CC 1-8 (Pharmacology)

IT 116666-63-8

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
(expression of L-type **calcium channel** with two different  $\beta$  subunits and modulation by Ro 40-5967)

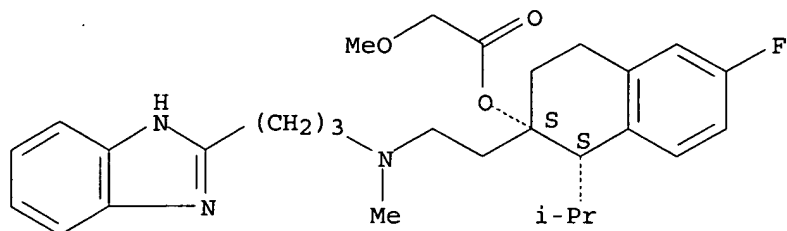
IT 116666-63-8

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
(expression of L-type **calcium channel** with two different  $\beta$  subunits and modulation by Ro 40-5967)

RN 116666-63-8 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 HCl

L103 ANSWER 43 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:683478 HCAPLUS

DOCUMENT NUMBER: 123:132374

TITLE: The binding interactions of Ro 40-5967 at the L-type Ca<sup>2+</sup> channel in cardiac tissue

AUTHOR(S): Rutledge, Aleta; Trigg, David J.

CORPORATE SOURCE: School of Pharmacy, State University of New York at Buffalo, Buffalo, NY, 14260, USA

SOURCE: European Journal of Pharmacology (1995), 280(2), 155-8

CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 19 Jul 1995

AB Ro 40-5967 [(1S,2S)-2-[2[[3-[2-benzamidopropyl]-methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthylmethoxyacetate] is a new Ca<sup>2+</sup> channel antagonist active at L-type channels. Radioligand binding studies in cardiac tissue show that Ro 40-5967 does not inhibit 1,4-dihydropyridine binding, but does inhibit diltiazem, desmethoxyverapamil and SR 33557 binding with IC<sub>50</sub> values of 8+10<sup>-9</sup>, 10<sup>-8</sup> and 5+10<sup>-8</sup> M, resp. Equilibrium and kinetic binding studies showed that Ro 40-5967 inhibited both desmethoxyverapamil and SR 33557 binding in an apparently competitive manner. Ro 40-5967 defines an addnl. and possibly unique antagonist binding site on the L-type voltage-gated Ca<sup>2+</sup> channel.

CC 1-8 (Pharmacology)

IT 116666-63-8

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(Ro 40-5967 binding interactions at L-type calcium channel in cardiac tissue)

IT 116666-63-8

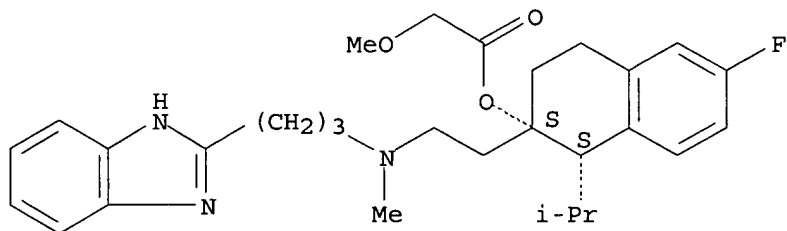
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(Ro 40-5967 binding interactions at L-type calcium channel in cardiac tissue)

RN 116666-63-8 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 HCl

L103 ANSWER 44 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:701621 HCAPLUS

DOCUMENT NUMBER: 123:74578

TITLE: Interaction of Ro 40-5967 and verapamil with the stably expressed  $\alpha_1$ -subunit of the cardiac L-type calcium channel

AUTHOR(S): Lacinova, Lubica; Welling, Andrea; Bosse, Eva; Ruth, Peter; Flockerzi, Veit; Hofmann, Franz

CORPORATE SOURCE: Inst. Pharmakol. Toxikol., Technischen Univ. Munich, Munich, 80802, Germany

SOURCE: Journal of Pharmacology and Experimental Therapeutics (1995), 274(1), 54-63

CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 26 Jul 1995

AB The interaction of the nondihydropyridine calcium channel antagonist Ro 40-5967 with the stably expressed class C  $\alpha_1$ -subunit of the cardiac L-type calcium channel was investigated and compared with that of verapamil by using the whole cell patch clamp configuration. Both compds. blocked the Ba<sup>++</sup> inward current. The IC<sub>50</sub> values at a holding potential of -80 or -40 mV were 4.9 and 1.4  $\mu$ M for Ro 40-5967 and 250 and 15.5  $\mu$ M for verapamil. Both Ro 40-5967 and verapamil induced a partial tonic block at a holding potential of -80 mV. The block increased with high depolarization rates. Both Ro 40-5967 and verapamil shifted the steady-state inactivation curve by more than 20 mV to hyperpolarized membrane potentials and decreased the inactivation rate constant. The effect of Ro 40-5967, but not that of verapamil, was attenuated by intracellular dialysis with GTP $\gamma$ S. The affinity for verapamil was not affected by replacing Ba<sup>++</sup> by Ca<sup>++</sup>, but was increased by the coexpression of the  $\beta_3$ -subunit. These results indicate that both compds. interact with high affinity with the inactivated channel state, but may interact addnl. with the open channel.

CC 1-8 (Pharmacology)

IT 52-53-9, Verapamil 116666-63-8

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES



(Uses)

(Ro 40-5967 and verapamil interaction with  $\alpha 1$ -subunit of cardiac L-type calcium channel)

IT 116666-63-8

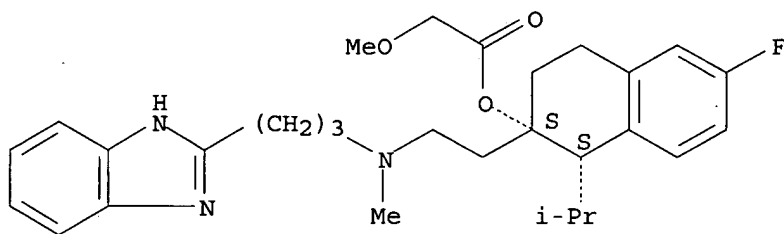
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(Ro 40-5967 and verapamil interaction with  $\alpha 1$ -subunit of cardiac L-type calcium channel)

RN 116666-63-8 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 HCl

L103 ANSWER 45 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:273684 HCAPLUS

DOCUMENT NUMBER: 122:46102

TITLE: The Ca<sup>++</sup>-channel blocker Ro 40-5967 blocks differently T-type and L-type Ca<sup>++</sup> channels

AUTHOR(S): Mehrke, G.; Zong, X. G.; Flockerzi, V.; Hofmann, F.

CORPORATE SOURCE: Institut fur Pharmakologie und Toxikologie der Technischen, Universitaet Muenchen, Muenchen, 80802, Germany

SOURCE: Journal of Pharmacology and Experimental Therapeutics (1994), 271(3), 1483-8

CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: Williams &amp; Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 05 Jan 1995

AB The effects of Ro 40-5967, a nondihydropyridine Ca<sup>++</sup> channel blocker, on low-voltage activated (T-type) and high-voltage activated (L-type) Ca<sup>++</sup> channels were compared. L-type barium currents were measured in Chinese hamster ovary cells stably transfected with the  $\alpha 1$  subunit of the class Cb Ca<sup>++</sup> channel. T-type barium currents were investigated in human medullary thyroid carcinoma cells. The Ba<sup>++</sup> currents of human medullary thyroid carcinoma cells were transient, activated at a threshold potential of -50 mV with the maximum at -14 mV and blocked by micromolar Ni<sup>++</sup>. The T- and L-type current inactivated with time constants of 33.4 and 416 ms at maximum barium currents, resp. Ro 40-5967 inhibited reversibly the T- and L-type currents with IC<sub>50</sub> values of 2.7 and 18.6  $\mu$ M, resp. The inhibition of the L-type current was voltage-dependent, whereas that of

the T-type current was not. Ro 40-5967 blocked T-type current already at a holding potential of -100 mV. The different types of block, i.e., voltage-dependent vs. tonic block, may contribute to the pharmacol. profile of Ro 40-5967 in intact animals.

CC 1-8 (Pharmacology)

IT 116666-63-8

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(Ca++-channel blocker Ro 40-5967 blocks differently

T-type and L-type Ca++ channels)

IT 116666-63-8

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

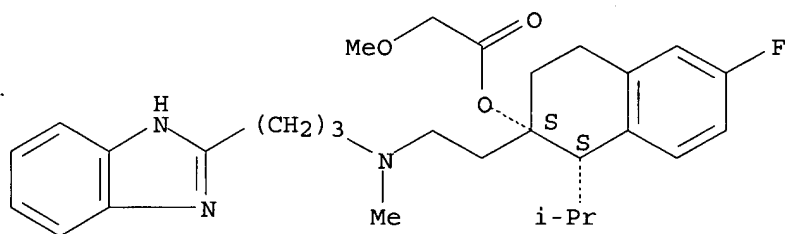
(Ca++-channel blocker Ro 40-5967 blocks differently

T-type and L-type Ca++ channels)

RN 116666-63-8 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 HCl

L103 ANSWER 46 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1994:671713 HCAPLUS

DOCUMENT NUMBER: 121:271713

TITLE: Effects of the calcium channel blockers, diltiazem and Ro 40-5967, on systemic hemodynamics and plasma noradrenaline levels in conscious dogs with pacing-induced heart failure

AUTHOR(S): Su, Jinbo; Renaud, Nathalie; Carayon, Alain; Crozatier, Bertrand; Hittinger, Luc; Laplace, Monique  
CORPORATE SOURCE: Laboratoire de Biochimie Medicale (A.C.), Paris, 75634, Fr.

SOURCE: British Journal of Pharmacology (1994), 113(2), 395-402  
CODEN: BJPCBM; ISSN: 0007-1188

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 10 Dec 1994

AB Calcium channel blockers increase cardiovascular morbidity and mortality in patients with left ventricular dysfunction. These adverse effects are probably related to the neg. inotropic effect of calcium channel blockers and/or a neurohormonal activation. The present study was designed to examine, in conscious dogs, the acute hemodynamic and sympathetic effects

of diltiazem and Ro 40-5967 (a novel calcium channel blocker) in the control state and in heart failure. Thirteen dogs were instrumented with a micromanometer and an aortic catheter. After completion of expts. in the control state, heart failure was induced by right ventricular pacing (250 beats min<sup>-1</sup>, 3 wk). Diltiazem and Ro 40-5967 were given i.v. (0.8 mg kg<sup>-1</sup> and 1.0 mg kg<sup>-1</sup> resp.). Cardiac output was measured by a thermodilution technique. In the control state, both agents decreased similarly mean aortic pressure with significant increases in heart rate, cardiac output (both +1.01 min<sup>-1</sup> and  $P < 0.001$ ) and plasma noradrenaline (both +55%) without changes in left ventricular dP/dtmax. In heart failure, for matched decreases in mean aortic pressure, neither diltiazem nor Ro 40-5967 changed heart rate significantly; diltiazem decreased cardiac output (-0.31 min<sup>-1</sup>,  $P < 0.02$ ) although the increased amount was smaller than in the control state. Plasma noradrenaline level was increased more during diltiazem infusion (+120%) than during Ro 40-5967 infusion (+38%,  $P < 0.001$ ). Diltiazem and Ro 40-5967 have similar hemodynamic and sympathetic effects in the control state. Heart failure alters hemodynamic and sympathetic responses to both calcium channel blockers but the magnitude of the alteration appears to be different. Diltiazem exerts a depressant effect on cardiac function which cannot be overcome by its vasodilator effect and sympathetic stimulation, while Ro 40-5967 has little effect on cardiac function. These data suggest that novel calcium channel blockers with less depressant effect may not be detrimental in heart failure.

CC 1-8 (Pharmacology)

IT 42399-41-7, Diltiazem 116666-63-8

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(calcium channel blockers diltiazem and Ro 40-5967

effect on systemic hemodynamics and plasma noradrenaline level in heart failure)

IT 116666-63-8

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

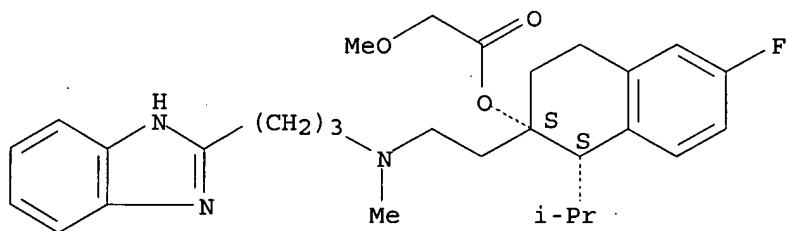
(calcium channel blockers diltiazem and Ro 40-5967

effect on systemic hemodynamics and plasma noradrenaline level in heart failure)

RN 116666-63-8 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 HCl

L103 ANSWER 47 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1994:692314 HCAPLUS

DOCUMENT NUMBER: 121:292314

TITLE: Effect of the calcium channel blockers S-, R-verapamil and Ro 40-5967 on adhesion and migration properties of lymphocytes acting on human vascular endothelium

AUTHOR(S): Blaheta, R.; Harder, S.; Hailer, N.; Scholz, M.; Bereiter-Hahn, J.; Encke, A.; Rietbrock, N.; Markus, B. H.

CORPORATE SOURCE: Dept. General Surgery, Hospital the J. W. Goethe-University Frankfurt, Frankfurt/Main, D-60590, Germany

SOURCE: Endothelium (1994), 1(4), 295-303

CODEN: ENDTE9; ISSN: 1062-3329

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 24 Dec 1994

AB The effects of the calcium channel blockers S- and R-verapamil or Ro 40-5967 on penetration processes of peripheral blood lymphocytes (PBL) added to allogenic human vascular endothelial cell (HUVEC) monolayers were studied. Both PBL adhesion and migration were evaluated by combined phase contrast and reflection interference contrast microscopy. PBL adhesion was inhibited by 22% when 100 µg/mL verapamil was added to the cell cultures. PBL migration was completely suppressed with verapamil concns. above 80 µg/mL (EC50: S-verapamil: 59.7 µg/mL, R-verapamil: 52.3 µg/mL). No differences were seen in the results obtained either with or without cytokine (γ-IFN or IL-1) stimulation. Ro 40-5967 reduced adhesion completely above concns. of 40 µg/mL. EC50 for migration was 13 ± 2 or 13 ± 1 µg/mL, resp. Immunohistochem. anal. of adhesion mol. expression on HUVEC revealed no inhibition of ICAM-1 and VCAM-1 by verapamil or Ro 40-5967. We concluded that the effects of the calcium channel blockers did not depend on cytokine stimulation and, as they were found similar for both verapamil enantiomers, also did not depend on the calcium channel blocking properties of the compds. Since adhesion mol. expression was not reduced on HUVEC the Ca<sup>2+</sup>-channel blockers tested in this assay seem to affect cellular infiltration via other pathways.

CC 1-8 (Pharmacology)

IT 36622-29-4, S-Verapamil 38321-02-7, (R)-Verapamil **116666-63-8**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(effect of **calcium channel** blockers S-, R-verapamil

and Ro 40-5967 on adhesion and migration properties of lymphocytes acting on human vascular endothelium)

IT **116666-63-8**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

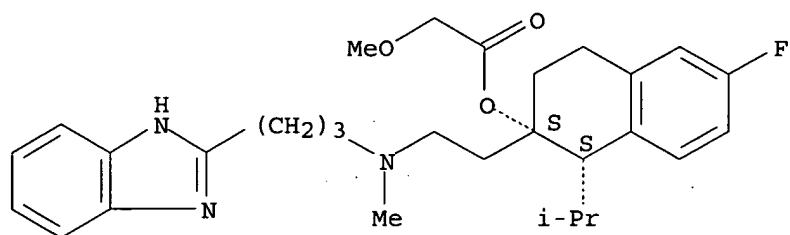
(effect of **calcium channel** blockers S-, R-verapamil

and Ro 40-5967 on adhesion and migration properties of lymphocytes acting on human vascular endothelium)

RN 116666-63-8 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 HCl

L103 ANSWER 48 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1994:692311 HCAPLUS

DOCUMENT NUMBER: 121:292311

TITLE: Chronic treatment with the Ca<sup>2+</sup> channel inhibitor RO 40-5967 potentiates endothelium-dependent relaxations in the aorta of the hypertensive salt sensitive Dahl rat

AUTHOR(S): Boulanger, Chantal M.; Desta, Barnabas; Clozel, Jean-Paul; Vanhoutte, Paul M.

CORPORATE SOURCE: Center for Experimental Therapeutics, Baylor College of Medicine, Houston, TX, 77030, USA

SOURCE: Blood Pressure (1994), 3(3), 193-6

CODEN: BLPREG; ISSN: 0803-7051

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 24 Dec 1994

AB Expts. were designed to determine whether or not chronic treatment with the Ca<sup>2+</sup> channel antagonist RO 40-5967 affects endothelium-dependent relaxations in the aorta of hypertensive, salt-sensitive Dahl rats. Salt-resistant and salt-sensitive Dahl rats were fed a diet containing 8% NaCl (for 8 wk); in each group, half of the animals were given RO 40-5967 chronically (0.4 mg/L; in the drinking water). RO 40-5967 lowered arterial blood pressure in the salt-sensitive, hypertensive, but not in the salt-resistant, normotensive rats. Rings, with and without endothelium, of thoracic aortas were suspended for isometric tension recording in conventional organ chambers. The chronic treatment with RO 40-5967 potentiated endothelium-dependent relaxations to acetylcholine, adenosine-diphosphate and thrombin in preps. from salt-sensitive, but not in those of salt-resistant Dahl rats. The treatment also augmented, in aortas from salt-sensitive animals, the relaxations of rings without endothelium to the donor of nitric oxide, SIN-1. These expts. demonstrate that chronic administration of RO 40-5967 potentiates endothelium-dependent relaxations in arteries from animals with salt-induced hypertension. This potentiation can be explained in part by an augmented sensitivity of the vascular smooth muscle to endothelium-derived nitric oxide.

CC 1-8 (Pharmacology)

IT 116666-63-8

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(calcium channel inhibitor RO 40-5967 potentiates endothelium-dependent relaxations in aorta of hypertensive salt sensitive rat)

IT 116666-63-8

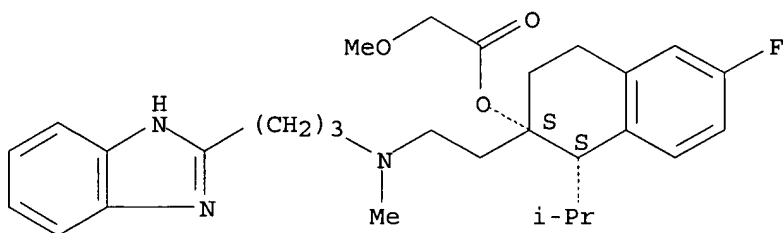
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(calcium channel inhibitor RO 40-5967 potentiates endothelium-dependent relaxations in aorta of hypertensive salt sensitive rat)

RN 116666-63-8 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 HCl

L103 ANSWER 49 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1994:289792 HCAPLUS

DOCUMENT NUMBER: 120:289792

TITLE: Resting state block and use independence of rat vascular muscle Ca++ channels by Ro 40-5967

AUTHOR(S): Mishra, Santosh K.; Hermsmeyer, Kent

CORPORATE SOURCE: Oregon Reg. Primate Res. Cent., Beaverton, OR, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics (1994), 269(1), 178-83

CODEN: JPETAB; ISSN: 0022-3565

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 11 Jun 1994

AB Blocking actions of the novel Ca++ antagonist, Ro 40-5967

{(1S,2S)-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride}, on divalent inward currents were characterized in spontaneously active vascular muscle cells (VMC) of neonatal rat azygos veins. Ca++ channel currents (ICa) were reduced by Ro 40-5967 in a concentration range from 0.1 to

10

μM, effective within the first 5 min of exposure. ICa were decreased by up to 70% during the first stimulus test pulse, remained constant during subsequent pulses, and were not shifted along the voltage axis, as determined by peak current-voltage plots. There was no change in apparent threshold or the voltage (+20 mV) at which maximum inward current occurred. Block of Ba++ currents through VMC Ca++ channels occurred independent of membrane potential, even when holding potential was as neg. as -80 mV. ICa were blocked to the same absolute values from holding potential = -30 mV. Thus, ICa block occurred equally during the first pulse and at all subsequent time points, i.e., under conditions in which VMC Ca++ channels were in the resting state, inactive state, or open state. To search further for

use-dependent effects of Ro 40-5967, the authors stimulated at higher frequencies (up to 0.3/s), but there was no change in fractional block with frequency or stimulus repetition and thus no use dependence of the block of VMC Ca<sup>++</sup> channels by Ro 40-5967. The blocking abilities of this new Ca<sup>++</sup> antagonist at physiol. resting potentials and under varying conditions of stimulation lead the authors to hypothesize that Ro 40-5967 causes an immediately maximal, tonic inhibition of VMC ICa, making it unusual among Ca<sup>++</sup> antagonists.

CC 1-8 (Pharmacology)

IT 116666-63-8

RL: BIOL (Biological study)

(L-type calcium channel blocking by, in vascular muscle cells, mechanism of)

IT 116666-63-8

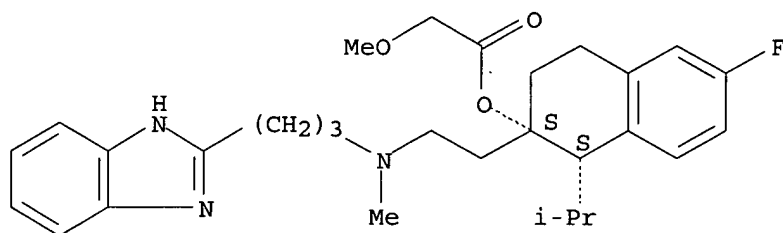
RL: BIOL (Biological study)

(L-type calcium channel blocking by, in vascular muscle cells, mechanism of)

RN 116666-63-8 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 HCl

L103 ANSWER 50 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1994:549028 HCAPLUS

DOCUMENT NUMBER: 121:149028

TITLE: Selective inhibition of T-type Ca<sup>2+</sup> channels by Ro 40-5967

AUTHOR(S): Mishra, Santosh K.; Hermesmeyer, Kent

CORPORATE SOURCE: Oregon Regional Primate Res. Cent., Beaverton, OR, 97006, USA

SOURCE: Circulation Research (1994), 75(1), 144-8

CODEN: CIRUAL; ISSN: 0009-7330

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 01 Oct 1994

AB The present study shows that the chemical novel nondihydropyridine Ca<sup>2+</sup> antagonist, Ro 40-5967, blocks T-type divalent ion currents in vascular muscle cells. T-type Ca<sup>2+</sup> channels were blocked selectively and completely by therapeutic concns. of 1 to 10 µmol/L Ro 40-5967, at which there was only 25% to 70% block of L-type Ca<sup>2+</sup> currents. Using the combination of Ro 40-5967 and nisoldipine, a dihydropyridine selective for L-type Ca<sup>2+</sup> channels, the authors found that all Ca<sup>2+</sup> current could be

completely blocked; thus, Ro 40-5967 is the first Ca<sup>2+</sup> channel blocker to eliminate dihydropyridine-insensitive voltage-dependent Ca<sup>2+</sup> current at therapeutically useful concns. The stepwise sequential block of T- and L-type Ca<sup>2+</sup> currents demonstrated in the present study fulfills the functional criterion for the sep. identity of the two Ca<sup>2+</sup> channel types, and introduces a pharmacol. tool that promises to be important in the exploration of T-type Ca<sup>2+</sup> channel function.

CC 1-12 (Pharmacology)

Section cross-reference(s): 13

IT 116666-63-8

RL: BIOL (Biological study)

(as T-type **calcium channel** blocker, in vascular smooth muscle)

IT 116666-63-8

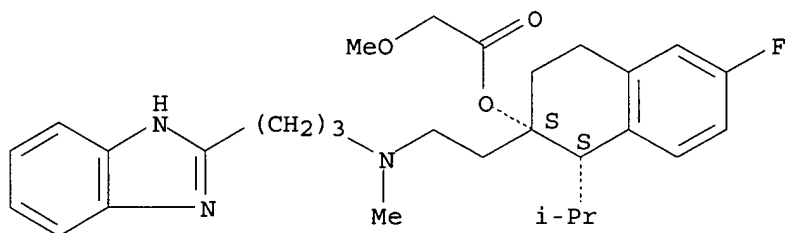
RL: BIOL (Biological study)

(as T-type **calcium channel** blocker, in vascular smooth muscle)

RN 116666-63-8 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 HCl

L103 ANSWER 51 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1994:692265 HCAPLUS

DOCUMENT NUMBER: 121:292265

TITLE: Modulation of adhesion molecule expression on endothelial cells by verapamil and other Ca<sup>++</sup> channel blockers

AUTHOR(S): Hailer, Nils P.; Blaheta, Roman A.; Harder, Sebastian; Scholz, Martin; Encke, Albrecht; Markus, Bernd H.

CORPORATE SOURCE: Department General Surgery, Hospital the Johann Wolfgang Goethe-University, Frankfurt/Main, Germany

SOURCE: Immunobiology (1994), 191(1), 38-51

CODEN: IMMND4; ISSN: 0171-2985

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 24 Dec 1994

AB Cytokine-induced expression of adhesion mols. on leukocytes and endothelial cells (EC) is a crucial point in the process of organ transplant rejection. It has been shown that protein kinase C (PKC) is involved in this activation process. Verapamil and other calcium channel blockers seem to possess immunosuppressive qualities in vivo and in vitro;



some authors suggested that this is due to PKC- or calmodulin-antagonism. Thus, our objectives were to further investigate the second-messenger systems involved in the stimulation of EC and to analyze whether the beneficial influence of calcium channel blockers on the outcome of transplantation is due to impaired expression of adhesion mol. on EC. Our results, obtained in an in vitro model using human umbilical vein EC, show that IL-1-induced expression of intercellular adhesion mol.-1 (ICAM-1) is in part mediated by PKC and that parallel activation of calmodulin is required. Expression of ICAM-1 was reduced to 38.5% by PKC-inhibitor H7 and to 77.2% by calmodulin-inhibitor W7. In addition, data on the intracellular events in TNF- $\alpha$ -induced expression of vascular cell adhesion mol.-1 (VCAM-1) is presented, showing that both PKC and, to a higher extent, calmodulin, are involved in this process. Expression of VCAM-1 was reduced to 63.7% by H7 and to 27.7% by W7. IL-1-induced expression of endothelial leukocyte adhesion mol.-1 (ELAM-1) is PKC-dependent but insensitive to blocking of calmodulin. Though activation of adhesion mol. expression utilizes PKC and/or calmodulin as second-messenger pathways the investigated calcium channel blockers verapamil (R- and S-enantiomers), diltiazem and Ro 40-5967 failed to inhibit adhesion mol. expression.

CC 1-7 (Pharmacology)

IT 36622-29-4, S-Verapamil 38321-02-7 42399-41-7, Diltiazem 65595-90-6, W7 84477-87-2, H7 116666-63-8

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(modulation of adhesion mol. expression on endothelial cells by verapamil and other **calcium channel** blockers)

IT 116666-63-8

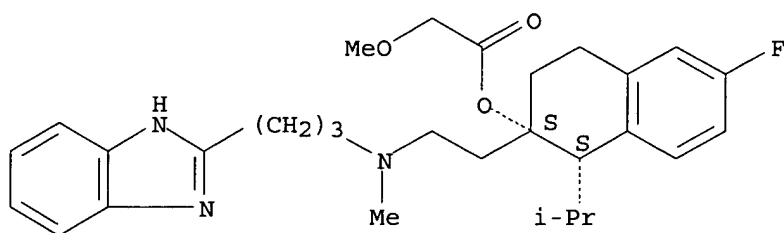
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(modulation of adhesion mol. expression on endothelial cells by verapamil and other **calcium channel** blockers)

RN 116666-63-8 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 HCl

L103 ANSWER 52 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1993:641133 HCAPLUS

DOCUMENT NUMBER: 119:241133

TITLE: Calcium channel actions of the non-dihydropyridine calcium channel antagonist Ro 40-5967 in vascular

muscle cells cultured from dog coronary and saphenous arteries

AUTHOR(S): Bian, Ka; Hermsmeyer, Kent

CORPORATE SOURCE: Earle A. Chiles Res. Inst., Oregon Health Sci. Univ., Portland, OR, 97201, USA

SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (1993), 348(2), 191-6  
CODEN: NSAPCC; ISSN: 0028-1298

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 11 Dec 1993

AB The authors studied the membrane effects of (1S,2S)-2-(2-[[3-(2(benzimidazolyl) propyl)methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl-methoxy-acetate dihydrochloride, Ro 40-5967, a new non-dihydropyridine (DHP) Ca<sup>2+</sup> channel antagonist, on dog coronary and saphenous arterial vascular muscle cells using the whole-cell patch-clamp method. Long-lasting (L-type) inward currents in 20 mM Ba<sup>2+</sup> were measured over a range of test potentials (300 ms) from -50 mV to +90mV from a holding potential of -80 mV in the presence of 1  $\mu$ M Bay k8644 (a DHP Ca<sup>2+</sup> agonist). Ro 40-5967 caused a concentration-dependent suppression of Ca<sup>2+</sup> channel currents in muscle cells from both arteries, with greater potency on coronary than saphenous arterial cells. The concentration of Ro 40-5967 which inhibited the magnitude of peak inward currents by 50% (IC<sub>50</sub>) was estimated to be 1  $\mu$ M (n = 5) in muscle cells from coronary artery and 10  $\mu$ M (n = 4) in saphenous artery. Ro 40-5967 (1  $\mu$ M) decreased the amplitude of the activation current-voltage relationship for coronary L-type Ca<sup>2+</sup> channel currents over a wider range of membrane potentials than verapamil, diltiazem, or nifedipine. In contrast, block of Ca<sup>2+</sup> channel currents in saphenous artery cells by 1  $\mu$ M Ro 40-5967 was only observed at command potentials pos. to 0 mV. Ro 40-5967 (1  $\mu$ M) significantly shifted the voltage-inactivation curve downward by 40% in coronary (n = 4), but only by 18% in saphenous arterial muscle cells (n = 3). The non-parallel shift of the coronary artery inactivation curve suggests that pronounced resting channel block is a notable feature of Ro 40-5967. The marked inhibition of Ba<sup>2+</sup> current by 1  $\mu$ M Ro 40-5967 in the inactivation protocol in coronary arterial muscle cells was found over the entire range of membrane holding potentials tested, while inhibition in the saphenous artery inactivation curve occurred only from holding potentials more pos. than -40 mV. Therefore, Ro 40-5967 is unique: 1) in acting over a wider range of voltages, on both instantaneous and resting Ca<sup>2+</sup> currents, than other Ca<sup>2+</sup> antagonists; 2) in producing more significant resting state block; and 3) in acting with selectivity for coronary over saphenous arteries.

CC 1-8 (Pharmacology)

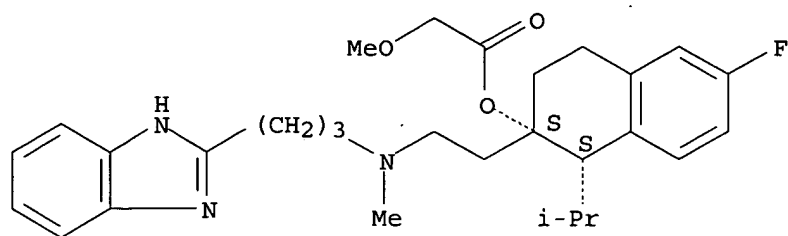
IT 116666-63-8  
RL: BIOL (Biological study)  
(calcium channel blocking by, in coronary and saphenous arteries)

IT 116666-63-8  
RL: BIOL (Biological study)  
(calcium channel blocking by, in coronary and saphenous arteries)

RN 116666-63-8 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl)methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 HCl

L103 ANSWER 53 OF 198 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1992:604926 HCAPLUS

DOCUMENT NUMBER: 117:204926

TITLE: Effect of calcium channel antagonists on the cardiac vagal tone response to submaximal exercise

AUTHOR(S): Billman, George E.; Halliwill, John R.; Avendano, Christopher E.

CORPORATE SOURCE: Dep. Physiol., Ohio State Univ., Columbus, OH, USA

SOURCE: Drug Development Research (1992), 27(2), 89-106

CODEN: DDREDK; ISSN: 0272-4391

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 28 Nov 1992

AB Redns. in cardiac vagal tone have been shown to correlate with a greater susceptibility to ventricular fibrillation. Calcium antagonists have been shown to protect against malignant arrhythmias probably as the result of direct actions on cardiac muscle. However, these drugs could also reflexively alter cardiac vagal tone as a consequence of redns. in arterial pressure. Therefore, the effects of various calcium channel antagonists on cardiac vagal tone, both at rest and during exercise, were investigated. The R-R interval was recorded in chronically instrumented mongrel dogs (n = 39) and the amplitude of the respiratory sinus arrhythmia (0.24-1.04 Hz) was calculated using time-series anal. techniques. Before exercise, verapamil (n = 17, 250 µg/kg), nifedipine (n = 5, 10 µg/kg; n = 9, 100 µg/kg), diltiazem (n = 10, 1,000 µg/kg), Ro 40-5967 (n = 14, 1,000 µg/kg), and magnesium sulfate (n = 10, 100 mg/kg) significantly increased heart rate, while flunarizine (n = 11, 2.5 mg/kg) and a lower dose of Ro 40-5967 (n = 5, 250 µg/kg) did not affect heart rate. During exercise, nifedipine (high dose) increased heart rate, while Ro 40-5967 (high dose) decreased heart rate. All six drugs reduced vagal tone before exercise; magnesium and nifedipine (high dose) elicited the greatest reduction, while flunarizine produced the smallest decrease. The vagal tone response to exercise was not affected by flunarizine and Ro 40-5967 (low dose), but it was accentuated by magnesium, nifedipine, and verapamil. Intermediate responses were noted for Ro-40-5967 (high dose) and diltiazem. Pronounced hemodynamic effects were noted for flunarizine, magnesium, nifedipine, and verapamil, but not for Ro-40-5967. Thus, calcium antagonists have variable hemodynamic profiles and can elicit pronounced redns. in cardiac vagal tone, presumably due to activation of the baroreceptor reflex.

CC 1-8 (Pharmacology)

IT 52-53-9, Verapamil 7487-88-9, Magnesium sulfate, biological studies

21829-25-4, Nifedipine 42399-41-7, Diltiazem 52468-60-7, Flunarizine  
**116666-63-8**

RL: BIOL (Biological study)  
 (exercise effect on **cardiac** vagal tone response to, as  
**calcium channel** antagonist)

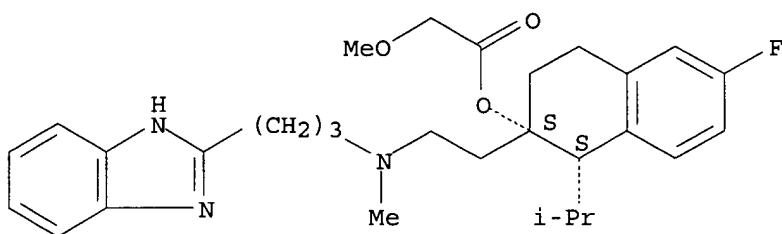
IT **116666-63-8**

RL: BIOL (Biological study)  
 (exercise effect on **cardiac** vagal tone response to, as  
**calcium channel** antagonist)

RN 116666-63-8 HCAPLUS

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 HCl

=> d ibib ab kwic hitstr 54-79

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, TOXCENTER, MEDLINE, BIOSIS, PASCAL, DRUGU, SCISEARCH, EMBASE, WPIX' - CONTINUE? (Y)/N:y

L103 ANSWER 54 OF 198 USPATFULL on STN DUPLICATE 4  
 ACCESSION NUMBER: 2003:188537 USPATFULL  
 TITLE: Materials and methods for the treatment of hypertension and angina  
 INVENTOR(S): Druzgala, Pascal, Santa Rosa, CA, UNITED STATES  
 Milner, Peter G., Los Altos Hills, CA, UNITED STATES  
 Pfister, Jurg, Los Altos, CA, UNITED STATES  
 Zhang, Xiaoming, Campbell, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003130330	A1	20030710
	US 6608097	B2	20030819
APPLICATION INFO.:	US 2002-269139	A1	20021010 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-328588P	20011010 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	SALIWANCHIK LLOYD & SALIWANCHIK, A PROFESSIONAL	

ASSOCIATION, 2421 N.W. 41ST STREET, SUITE A-1,  
GAINESVILLE, FL, 326066669

NUMBER OF CLAIMS: 33  
EXEMPLARY CLAIM: 1  
NUMBER OF DRAWINGS: 12 Drawing Page(s)  
LINE COUNT: 790

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The subject invention provides useful and novel calcium channel blockers based upon mibefradil. The subject invention also provides methods for synthesizing the compounds of the invention. The invention also provides methods for the control or prevention of hypertension, angina pectoris, ischemia, arrhythmias, and cardiac insufficiency in a patient by administering a compound, or composition, of the invention to an individual in need of such treatment.

PRAI US 2001-328588P 20011010 (60) <--

ST mibefradil deriv **calcium channel** blocker therapeutic;  
**hypertension** mibefradil deriv **calcium channel**  
blocker; **angina** mibefradil deriv **calcium**  
**channel** blocker; **ischemia** mibefradil deriv  
**calcium channel** blocker; **arrhythmia**  
mibefradil deriv **calcium channel** blocker;  
**cardiac** insufficiency mibefradil deriv **calcium**  
**channel** blocker

IT **Heart, disease**  
(**angina pectoris**; mibefradil-based compds. as **calcium**  
**channel** blockers for treatment of **hypertension** and  
**angina**)

IT **Heart, disease**  
(**arrhythmia**; mibefradil-based compds. as **calcium**  
**channel** blockers for treatment of **hypertension** and  
**angina**)

IT **Ion channel** blockers  
(**calcium**; mibefradil-based compds. as **calcium**  
**channel** blockers for treatment of **hypertension** and  
**angina**)

IT **Heart, disease**  
(**failure**; mibefradil-based compds. as **calcium channel**  
blockers for treatment of **hypertension** and **angina**)

IT **Liver**  
(**liver function test**; mibefradil-based compds. as **calcium**  
**channel** blockers for treatment of **hypertension** and  
**angina**)

IT **Enzymes, biological studies**  
(**metabolic, non-oxidative**; mibefradil-based compds. as **calcium**  
**channel** blockers for treatment of **hypertension** and  
**angina**)

IT **Drug interactions**  
(**metabolic**; mibefradil-based compds. as **calcium**  
**channel** blockers for treatment of **hypertension** and  
**angina**)

IT **Anti-ischemic** agents

IT **Antiarrhythmics**

IT **Antihypertensives**

IT **Cardiovascular** agents

IT **Drug delivery** systems

IT **Drug metabolism**

IT **Human**

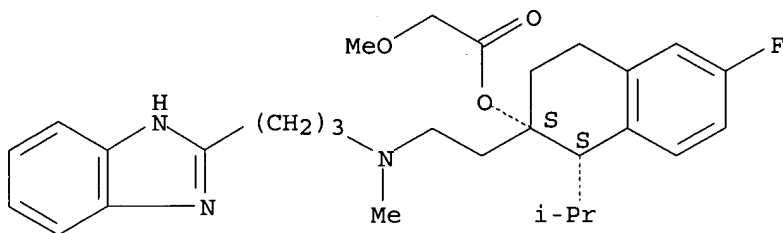
IT **Hypertension**

IT **Ischemia**

IT **Pharmacokinetics**

(mibefradil-based compds. as **calcium channel**  
blockers for treatment of **hypertension** and **angina**)  
IT 9027-41-2, Hydrolase 9035-51-2, Cytochrome P 450, biological studies  
(mibefradil-based compds. as **calcium channel**  
blockers for treatment of **hypertension** and **angina**)  
IT 116644-53-2D, Mibefradil, derivs.  
(mibefradil-based compds. as **calcium channel**  
blockers for treatment of **hypertension** and **angina**)  
IT 116644-53-2D, Mibefradil, derivs.  
(mibefradil-based compds. as **calcium channel**  
blockers for treatment of **hypertension** and **angina**)  
RN 116644-53-2 USPATFULL  
CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 55 OF 198 USPATFULL on STN DUPLICATE 5  
ACCESSION NUMBER: 2003:10326 USPATFULL  
TITLE: Methods for remodeling neuronal and cardiovascular pathways  
INVENTOR(S): Adams, Michael A., Kingston, CANADA  
Heaton, Jeremy P.W., Gananoque, CANADA  
PATENT ASSIGNEE(S): Queen's University of Kingston, Kingston, CANADA  
(non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003008020	A1	20030109
	US 6787553	B2	20040907
APPLICATION INFO.:	US 2002-192281	A1	20020709 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2001-902787, filed on 12 Jul 2001, GRANTED, Pat. No. US 6458797 Division of Ser. No. US 1999-382749, filed on 25 Aug 1999, GRANTED, Pat. No. US 6284763		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-98178P	19980826 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834	
NUMBER OF CLAIMS:	33	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	6 Drawing Page(s)	
LINE COUNT:	1035	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		

AB The present invention provides a method of administration of an agent which acts to remodel neuronal or vascular pathways for the long term management of sexual dysfunction in both males and females. In a preferred embodiment, the invention provides a method of ameliorating or reversing pathogenic vascular degradative modeling in the ilio-hypogastric-pudendal arterial bed and genitalia comprising administering to a human patient in need of such treatment a therapeutically effective amount of an anti-pressor agent. The anti-pressor agent comprises one or more compounds selected from the therapeutic classes of direct vasodilators such as hydralazine and NO donors, ACE inhibitors, angiotensin-II receptor antagonists,  $\alpha$ .sub.1-adrenergic receptor antagonists,  $\beta$ -adrenergic receptor antagonists, calcium channel blockers, and phosphodiesterase inhibitors. The anti-pressor agent may be co-administered with a diuretic compound, and is administered either chronically at low dose, or for short periods of time at doses higher than are typically used for the treatment of hypertension. In certain embodiments of the method of the invention, the anti-pressor agent is co-administered with a diuretic agent and/or prostaglandin-E.sub.1.

PRAI US 1998-98178P 19980826 (60) <--

ST antipressor **cardiovascular** neuronal remodeling sexual dysfunction; diuretic antipressor **cardiovascular** neuronal remodeling sexual dysfunction; prostaglandin antipressor **cardiovascular** neuronal remodeling sexual dysfunction

IT Angiotensin receptors  
(AT1, antagonists; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)

IT Antihypertensives

IT **Cardiovascular** agents

IT Diuretics

IT Nervous system agents

IT Reproductive tract

IT Vasodilators  
(anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)

IT Ion **channel** blockers  
(**calcium**; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)

IT Sexual behavior  
(disorder; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)

IT Artery  
(ilio-hypogastric-pudendal arterial bed; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)

IT Blood vessel  
(pathogenic vascular degradative modeling; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)

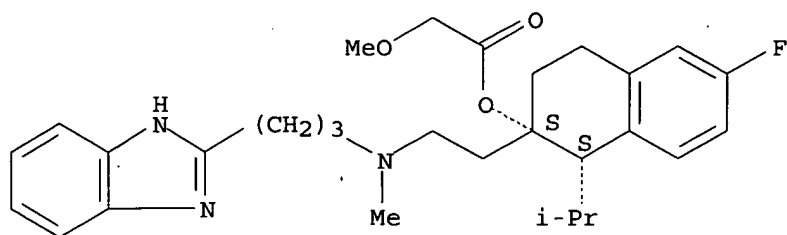
IT Penis  
(penile vascular bed; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)

IT Adrenoceptor antagonists  
( $\alpha$ 1-; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual

- dysfunction)
- IT Adrenoceptor antagonists  
( $\beta$ -; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT 9012-42-4, Adenyl cyclase 9054-75-5, Guanylyl cyclase  
(activators; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT 10102-43-9, Nitric oxide, biological studies  
(and NO donors; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT 390-28-3, Methoxamine 11000-17-2, Vasopressin 11128-99-7, Angiotensin II  
(anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT 50-60-2, Phentolamine 52-53-9, Verapamil 55-63-0, Glyceryl trinitrate 59-96-1, Phenoxybenzamine 78-11-5, Pentaerythritol tetranitrate 86-54-4, Hydralazine 87-33-2, Isosorbide dinitrate 745-65-3, Prostaglandin E1 835-31-4, Naphazoline 4205-90-7, Clonidine 14402-89-2, Sodium nitroprusside 16051-77-7, Isosorbide 5-mononitrate 19216-56-9, Prazosin 21829-25-4, Nifedipine 25717-80-0, Molsidomine 26844-12-2, Indoramin 33876-97-0, 3-Morpholinolinosydnonimine 34661-75-1, Urapidil 35795-16-5, Trimazosin 36894-69-6 42399-41-7, Diltiazem 42794-76-3, Midodrine 53054-07-2 55985-32-5, Nicardipine 57564-91-7, S-Nitrosoglutathione 60719-84-8, Amrinone 62571-86-2, Captopril 63590-64-7, Terazosin 64706-54-3, Bepridil 66085-59-4, Nimodipine 66575-29-9, Forskolin 66711-21-5, Apraclonidine 72822-12-9, Dapiprazole 72956-09-3, Carvedilol 74191-85-8, Doxazosin 74258-86-9, Alacepril 75847-73-3, Enalapril 76547-98-3, Lisinopril 79032-48-7, S-Nitroso-N-acetylpenicillamine 80755-51-7, Bunazosin 81403-80-7, Alfuzosin 82834-16-0, Perindopril 82924-03-6, Pentopril 83435-66-9, Delapril 83647-97-6, Spirapril 85441-61-8, Quinapril 85856-54-8, Moveltipril 86541-75-5, Benazepril 87333-19-5, Ramipril 87679-37-6, Trandolapril 88768-40-5, Cilazapril 89371-37-9, Imidapril 98048-97-6, Fosinopril 103775-10-6, Moexipril 103890-78-4, Lacidipine 106133-20-4, Tamsulosin 109214-55-3, Libenzapril 111223-26-8, Ceronapril 111902-57-9, Temocapril 114798-26-4, Losartan **116644-53-2**, Mibefradil 133040-01-4, Eprosartan 137862-53-4, Valsartan 138402-11-6, Irbesartan 139755-83-2, Sildenafil 170632-47-0, YC-1  
(anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT 9015-82-1 9025-82-5, Phosphodiesterase  
(inhibitors; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT **116644-53-2**, Mibefradil  
(anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- RN 116644-53-2 USPATFULL
- CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.





L103 ANSWER 56 OF 198    USPATFULL on STN    DUPLICATE 6  
 ACCESSION NUMBER:    2002:61232    USPATFULL  
 TITLE:    Methods for remodeling neuronal and cardiovascular pathways  
 INVENTOR(S):    Adams, Michael A., Kingston, CANADA  
                   Heaton, Jeremy P.W., Gananoque, CANADA

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002035067	A1	20020321
	US 6458797	B2	20021001
APPLICATION INFO.:	US 2001-902787	A1	20010712 (9) <--
RELATED APPLN. INFO.:	Division of Ser. No. US 1999-382749, filed on 25 Aug 1999, GRANTED, Pat. No. US 6284763		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-98178P	19980826 (60) <--
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	PARTEQ Innovations, Queen's University, Biosciences Complex, Room 1625, Kingston, ON, K7L 3N6	
NUMBER OF CLAIMS:	33	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	6 Drawing Page(s)	
LINE COUNT:	1037	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a method of administration of an agent which acts to remodel neuronal or vascular pathways for the long term management of sexual dysfunction in both males and females. In a preferred embodiment, the invention provides a method of ameliorating or reversing pathogenic vascular degradative modeling in the ilio-hypogastric-pudendal arterial bed and genitalia comprising administering to a human patient in need of such treatment a therapeutically effective amount of an anti-pressor agent. The anti-pressor agent comprises one or more compounds selected from the therapeutic classes of direct vasodilators such as hydralazine and NO donors, ACE inhibitors, angiotensin-II receptor antagonists,  $\alpha$ .sub.1-adrenergic receptor antagonists,  $\beta$ -adrenergic receptor antagonists, calcium channel blockers, and phosphodiesterase inhibitors. The anti-pressor agent may be co-administered with a diuretic compound, and is administered either chronically at low dose, or for short periods of time at doses higher than are typically used for the treatment of hypertension. In certain embodiments of the method of the invention, the anti-pressor agent is co-administered with a diuretic agent and/or prostaglandin-E.sub.1.

AI	US 2001-902787	A1	20010712 (9)	<--
PRAI	US 1998-98178P		19980826 (60)	<--

- ST antipressor **cardiovascular** neuronal remodeling sexual dysfunction; diuretic antipressor **cardiovascular** neuronal remodeling sexual dysfunction; prostaglandin antipressor **cardiovascular** neuronal remodeling sexual dysfunction
- IT Angiotensin receptors  
(AT1, antagonists; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT Antihypertensives
- IT **Cardiovascular** agents
- IT Diuretics
- IT Nervous system agents
- IT Reproductive tract
- IT Vasodilators  
(anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT Ion **channel** blockers  
(**calcium**; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT Sexual behavior  
(disorder; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT Artery  
(ilio-hypogastric-pudendal arterial bed; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT Blood vessel  
(pathogenic vascular degradative modeling; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT Penis  
(penile vascular bed; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT Adrenoceptor antagonists  
( $\alpha$ 1-; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT Adrenoceptor antagonists  
( $\beta$ -; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT 9012-42-4, Adenyl cyclase 9054-75-5, Guanylyl cyclase  
(activators; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT 10102-43-9, Nitric oxide, biological studies  
(and NO donors; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT 390-28-3, Methoxamine 11000-17-2, Vasopressin 11128-99-7, Angiotensin II  
(anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT 50-60-2, Phentolamine 52-53-9, Verapamil 55-63-0, Glyceryl trinitrate 59-96-1, Phenoxylbenzamine 78-11-5, Pentaerythritol tetranitrate

86-54-4, Hydralazine 87-33-2, Isosorbide dinitrate 745-65-3,  
 Prostaglandin E1 835-31-4, Naphazoline 4205-90-7, Clonidine  
 14402-89-2, Sodium nitroprusside 16051-77-7, Isosorbide 5-mononitrate  
 19216-56-9, Prazosin 21829-25-4, Nifedipine 25717-80-0, Molsidomine  
 26844-12-2, Indoramin 33876-97-0, 3-Morpholinostyrene 34661-75-1,  
 Urapidil 35795-16-5, Trimazosin 36894-69-6 42399-41-7, Diltiazem  
 42794-76-3, Midodrine 53054-07-2 55985-32-5, Nicardipine  
 57564-91-7, S-Nitrosoglutathione 60719-84-8, Amrinone 62571-86-2,  
 Captopril 63590-64-7, Terazosin 64706-54-3, Bepridil 66085-59-4,  
 Nimodipine 66575-29-9, Forskolin 66711-21-5, Apraclonidine  
 72822-12-9, Dapiprazole 72956-09-3, Carvedilol 74191-85-8, Doxazosin  
 74258-86-9, Alacepril 75847-73-3, Enalapril 76547-98-3, Lisinopril  
 79032-48-7, S-Nitroso-N-acetylpenicillamine 80755-51-7, Bunazosin  
 81403-80-7, Alfuzosin 82834-16-0, Perindopril 82924-03-6, Pentopril  
 83435-66-9, Delapril 83647-97-6, Spirapril 85441-61-8, Quinapril  
 85856-54-8, Moveltipril 86541-75-5, Benazepril 87333-19-5, Ramipril  
 87679-37-6, Trandolapril 88768-40-5, Cilazapril 89371-37-9, Imidapril  
 98048-97-6, Fosinopril 103775-10-6, Moexipril 103890-78-4, Lacidipine  
 106133-20-4, Tamsulosin 109214-55-3, Libenzapril 111223-26-8,  
 Ceronapril 111902-57-9, Temocapril 114798-26-4, Losartan  
 116644-53-2, Mibefradil 133040-01-4, Eprosartan 137862-53-4,  
 Valsartan 138402-11-6, Irbesartan 139755-83-2, Sildenafil  
 170632-47-0, YC-1

(anti-pressor agents and methods for remodeling neuronal and  
**cardiovascular** pathways for long term management of sexual  
 dysfunction)

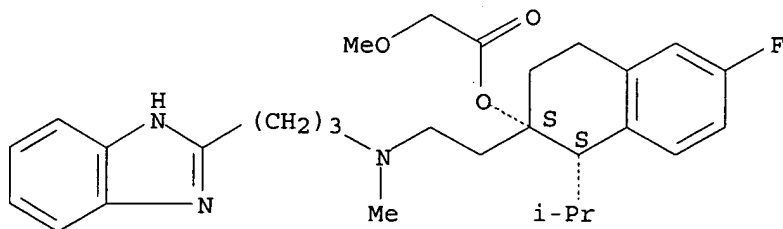
IT 9015-82-1 9025-82-5, Phosphodiesterase  
 (inhibitors; anti-pressor agents and methods for remodeling neuronal  
 and **cardiovascular** pathways for long term management of  
 sexual dysfunction)

IT 116644-53-2, Mibefradil  
 (anti-pressor agents and methods for remodeling neuronal and  
**cardiovascular** pathways for long term management of sexual  
 dysfunction)

RN 116644-53-2 USPATFULL

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-  
 yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-  
 methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 57 OF 198 USPATFULL on STN DUPLICATE 7  
 ACCESSION NUMBER: 2001:205937 USPATFULL  
 TITLE: Tetrahydronaphthalene derivatives and their use  
 INVENTOR(S): Li, Ming, Mobile, AL, United States  
 Hansen, John Bondo, Jyderup, Denmark  
 Tagmose, Tina Moller, Ballerup, Denmark

NUMBER KIND DATE

```

PATENT INFORMATION:  US 2001041730      A1    20011115      <--
                     US 6410743        B2    20020625
APPLICATION INFO.:   US 2001-818392      A1    20010327  (9)      <--
RELATED APPLN. INFO.: Continuation of Ser. No. WO 2001-DK129, filed on 23 Feb
                     2001, UNKNOWN

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                     NUMBER      DATE
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PRIORITY INFORMATION: DK 2000-294      20000225      <--
                     US 2000-185294P   20000228  (60)      <--
DOCUMENT TYPE:       Utility
FILE SEGMENT:        APPLICATION
LEGAL REPRESENTATIVE: Steve T. Zelson, Esq., Novo Nordisk of North America,
                     Inc., Suite 6400, 405 Lexington Avenue, New York, NY,
                     10174-6401
NUMBER OF CLAIMS:    18
EXEMPLARY CLAIM:     1
LINE COUNT:          648

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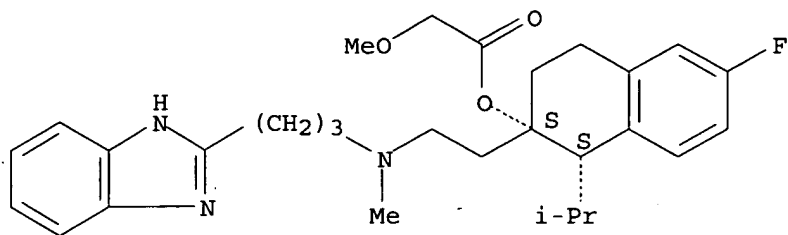
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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AB    Tetrahydronaphthalene derivatives, and compositions comprising the
      compounds. The tetrahydronaphthalene derivates are useful in inhibiting
      a rise in intracellular calcium mediated by an influx through T-type
      calcium channels, and are thus useful for treatment of, for example,
      type 1 and type 2 diabetes and cardiovascular diseases associated with
      diabetes.
PI    US 2001041730      A1    20011115      <--
      US 6410743        B2    20020625
AI    US 2001-818392      A1    20010327  (9)      <--
PRAI  DK 2000-294        20000225      <--
PRAI  US 2000-185294P    20000228  (60)      <--
IT    Heart, disease
      (infarction, macrovascular diseases associated with; preparation of
      tetrahydronaphthalene derivs. for use in therapy of type 1 and type 2
      diabetes)
IT    4023-34-1, Cyclopropanecarbonyl chloride 116666-63-8,
      Mibefradil dihydrochloride
      (preparation of tetrahydronaphthalene derivs. for use in therapy of type 1
      and type 2 diabetes)
IT    116666-63-8, Mibefradil dihydrochloride
      (preparation of tetrahydronaphthalene derivs. for use in therapy of type 1
      and type 2 diabetes)
RN    116666-63-8  USPATFULL
CN    Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-
      yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-
      methylethyl)-2-naphthalenyl ester, dihydrochloride (9CI)  (CA INDEX
      NAME)

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Absolute stereochemistry.



● 2 HCl

L103 ANSWER 58 OF 198    USPATFULL on STN    DUPLICATE 8  
 ACCESSION NUMBER:    2001:231283    USPATFULL  
 TITLE:    Nitrosated and nitrosylated phosphodiesterase inhibitors, compositions and methods of use  
 INVENTOR(S):    Garvey, David S., Dover, MA, United States  
                   de Tejada, Inigo Saenz, Madrid, Spain  
                   Earl, Richard A., Westford, MA, United States  
                   Khanapure, Subhash P., Clinton, MA, United States  
 PATENT ASSIGNEE(S):    NitroMed, Inc., Bedford, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6331543	B1	20011218
APPLICATION INFO.:	US 1999-387727		19990901 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1998-145142, filed on 1 Sep 1998, now patented, Pat. No. US 5958926		
	Continuation-in-part of Ser. No. US 1996-740764, filed on 1 Nov 1996, now patented, Pat. No. US 5874437		
	Continuation-in-part of Ser. No. WO 1997-US19870, filed on 31 Oct 1997		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	GRANTED		
PRIMARY EXAMINER:	Raymond, Richard L.		
LEGAL REPRESENTATIVE:	Hale and Dorr LLP		
NUMBER OF CLAIMS:	94		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	60 Drawing Figure(s); 60 Drawing Page(s)		
LINE COUNT:	4847		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB    The present invention describes novel nitrosated and/or nitrosylated phosphodiesterase inhibitors, and novel compositions containing at least one nitrosated and/or nitrosylated phosphodiesterase inhibitor, and, optionally, one or more compounds that donate, transfer or release nitric oxide, elevate endogenous levels of endothelium-derived relaxing factor, stimulate endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase and/or one or more vasoactive agents. The present invention also provides novel compositions containing at least one phosphodiesterase inhibitor, and one or more compounds that donate, transfer or release nitric oxide, elevate endogenous levels of endothelium-derived relaxing factor, stimulate endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase and/or one or more vasoactive agents. The present invention also provides methods for

treating or preventing sexual dysfunctions in males and females, for enhancing sexual responses in males and females, and for treating or preventing diseases induced by the increased metabolism of cyclic guanosine 3',5'-monophosphate (cGMP), such as hypertension, pulmonary hypertension, congestive heart failure, renal failure, myocardial infarction, stable, unstable and variant (Prinzmetal) angina, atherosclerosis, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, asthma, bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, dementia, immunodeficiency, premature labor, dysmenorrhoea, benign prostatic hyperplasia (BPH), bladder outlet obstruction, incontinence, conditions of reduced blood vessel patency, e.g., postpercutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, allergic rhinitis, glaucoma, and diseases characterized by disorders of gut motility, e.g., irritable bowel syndrome (IBS).

PI	US 6331543	B1	20011218	<--
REP	US 4308278	Dec 1981	424/273.000	Schneider et al.
	US 4963541	Oct 1990	514/183.000	Brooks et al.
	US 5171217	Dec 1992	604/053.000	March et al.
	US 5190967	Mar 1993	514/411.000	Riley
	US 5196426	Mar 1993	514/258.000	Saccomano et al.
	US 5223504	Jun 1993	514/263.000	Noverola et al.
	US 5254575	Oct 1993	514/365.000	Pick et al.
	US 5340827	Aug 1994	514/352.000	Beeley et al.
	US 5380758	Jan 1995	514/562.000	Stamler et al.
	US 5426107	Jun 1995	514/234.200	Bell et al.
	US 5438060	Aug 1995	514/258.000	Miyazaki et al.
	US 5439938	Aug 1995	514/565.000	Snyder et al.
	US 5491147	Feb 1996	514/247.000	Boyd et al.
	US 5492911	Feb 1996	514/252.000	Stief
	US 5543430	Aug 1996	514/565.000	Kaesemeyer
	US 5545647	Aug 1996	514/343.000	Tanaka et al.
	US 5565466	Oct 1996	514/280.000	Gioco et al.
	US 5583101	Dec 1996	514/002.000	Stamler et al.
	US 5614627	Mar 1997	544/293.000	Takase et al.
	US 5618814	Apr 1997	514/234.200	Heckel et al.
	US 5645839	Jul 1997	424/400.000	Chobanian et al.
	US 5646181	Jul 1997	514/506.000	Fung et al.
	US 5698589	Dec 1997	514/509.000	Allen
	US 5716993	Feb 1998	514/619.000	Ozaki et al.
	US 5731339	Mar 1998	514/400.000	Lowrey
	US 5767160	Jun 1998	514/565.000	Kaesemeyer
	US 5824669	Oct 1998	514/174.000	Garvey et al.
	US 5849741	Dec 1998	514/248.000	Watanabe et al.
	US 5859006	Jan 1999	514/249.000	Daugan
	US 5869516	Feb 1999	514/404.000	Arlt et al.
	US 5877216	Mar 1999	514/573.000	Place et al.
	US 5932538	Aug 1999	514/002.000	Garvey et al.
	US 5958926	Sep 1999	514/253.000	Garvey et al.
	US 5973011	Oct 1999	514/742.000	Noack et al.
	US 5981527	Nov 1999	514/250.000	Daugan et al.
	US 6007824	Dec 1999	424/195.100	Duckett et al.
	US 6037346	Mar 2000	514/258.000	Doherty, Jr. et al.
	US 6143746	Nov 2000	514/249.000	Daugan et al.
	EP 252721	Jan 1988		
	EP 352960	Jan 1990		
	EP 442204	Aug 1991		
	EP 463756	Jan 1992		
	EP 506194	Sep 1992		
	FR 2547501	Dec 1984		

WO 9307149 Apr 1993  
 WO 9312068 Jun 1993  
 WO 9501338 Jan 1995  
 WO 9509636 Apr 1995  
 WO 9526725 Oct 1995  
 WO 9625184 Aug 1996  
 WO 9703675 Feb 1997  
 WO 9703985 Feb 1997  
 WO 9734871 Sep 1997  
 WO 9739760 Oct 1997  
 WO 9743287 Nov 1997  
 WO 9817668 Apr 1998  
 WO 9819672 May 1998  
 WO 9852569 Nov 1998  
 WO 9849166 Nov 1998  
 WO 9921558 May 1999  
 WO 9921562 May 1999  
 WO 9922731 May 1999  
 WO 9930697 Jun 1999

RLI Continuation-in-part of Ser. No. US 1998-145142, filed on 1 Sep 1998,  
 now patented, Pat. No. US. . . .  
 PI US 6331543 B1 20011218 <--  
 AI US 1999-387727 19990901 (9) <--  
 IT Edema  
 (cardiac; synthesis of nitrosated and nitrosylated  
 (hetero)cyclic phosphodiesterase inhibitors used in treatment of sexual  
 dysfunction)  
 IT Calcium channel blockers  
 IT Dopamine agonists  
 IT Opioid antagonists  
 IT Potassium channel openers  
 IT Vasodilators  
 (combination pharmaceutical; synthesis of nitrosated and nitrosylated  
 (hetero)cyclic phosphodiesterase inhibitors used in treatment of sexual  
 dysfunction)  
 IT Heart, disease  
 (edema; synthesis of nitrosated and nitrosylated (hetero)cyclic  
 phosphodiesterase inhibitors used in treatment of sexual dysfunction)  
 IT Heart, disease  
 (infarction; synthesis of nitrosated and nitrosylated (hetero)cyclic  
 phosphodiesterase inhibitors used in treatment of sexual dysfunction)  
 IT Hypertension  
 (pulmonary; synthesis of nitrosated and nitrosylated (hetero)cyclic  
 phosphodiesterase inhibitors used in treatment of sexual dysfunction)  
 IT 56-85-9, L-Glutamine, biological studies 58-32-2D, Dipyridamole,  
 nitroso derivs. 58-55-9D, Theophylline, nitroso derivs. 70-26-8,  
 L-Ornithine 74-79-3, L-Arginine, biological studies 74-79-3D,  
 L-Arginine, nitroso derivs. 156-86-5, L-Homoarginine 372-75-8,  
 Citrulline 6493-05-6D, Pentoxifylline, nitroso derivs. 35135-01-4D,  
 Benafentrine, nitroso derivs. 37762-06-4D, Zaprinst, nitroso derivs.  
 51209-75-7, S-Nitroso-cysteine 56577-02-7, S-Nitroso-N-acetylcysteine  
 57076-71-8D, Denbufylline, nitroso derivs. 57564-91-7,  
 S-Nitrosoglutathione 59893-86-6 59893-86-6D, nitroso derivs.  
 61413-54-5D, Rolipram, nitroso derivs. 69592-38-7D, nitroso derivs.  
 69592-58-1D, nitroso derivs. 69592-59-2D, nitroso derivs.  
 69975-86-6D, Doxofylline, nitroso derivs. 78415-72-2D, Milrinone,  
 nitroso derivs. 79032-48-7, S-Nitroso-N-acetylpenicillamine  
 81840-15-5D, Vesnarinone, nitroso derivs. 84243-58-3D, Imazodan,  
 nitroso derivs. 84490-12-0D, Piroximone, nitroso derivs. 86798-59-6D,  
 CI 930, nitroso derivs. 87164-90-7D, ICI 153110, nitroso derivs.

90697-57-7D, Motapizone, nitroso derivs. 94192-59-3D, Lixazinone, nitroso derivs. 98326-33-1D, MCI-154, nitroso derivs. 102669-89-6D, Saterinone, nitroso derivs. 102791-47-9D, Nanterinone, nitroso derivs. 106730-54-5D, Loprinone, nitroso derivs. 107189-96-8D, MS 857, nitroso derivs. 107767-55-5D, Albifylline, nitroso derivs. 112127-66-9D, nitroso derivs. 115344-47-3D, Siguzodan, nitroso derivs. 116666-63-8D, Posicor, nitroso derivs. 120223-04-3D, EMD 53998, nitroso derivs. 122130-63-6, S-Nitroso-captopril 132225-86-6D, WIN 62582, nitroso derivs. 139308-65-9D, Tolafentrine, nitroso derivs. 139427-42-2, S-Nitroso-homocysteine 139755-83-2D, Sildenafil, nitroso derivs. 141184-34-1D, Filaminast, nitroso derivs. 143343-83-3D, Toborinone, nitroso derivs. 144035-83-6D, Piclamilast, nitroso derivs. 144967-96-4D, WIN 63291, nitroso derivs. 145261-31-0D, Org 20241, nitroso derivs. 162401-32-3D, Roflumilast, nitroso derivs. 380375-18-8D, nitroso derivs.

(synthesis of nitrosated and nitrosylated (hetero)cyclic phosphodiesterase inhibitors used in treatment of sexual dysfunction)

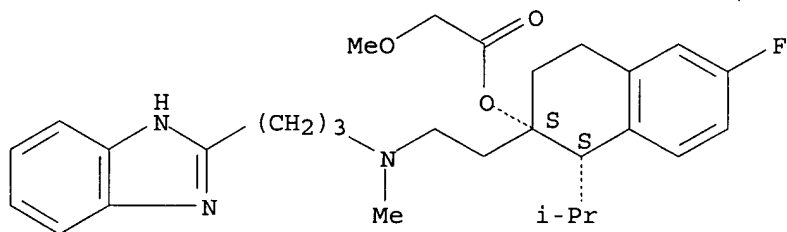
IT 116666-63-8D, Posicor, nitroso derivs.

(synthesis of nitrosated and nitrosylated (hetero)cyclic phosphodiesterase inhibitors used in treatment of sexual dysfunction)

RN 116666-63-8 USPATFULL

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 HCl

L103 ANSWER 59 OF 198 USPATFULL on STN  
 ACCESSION NUMBER: 2004:298756 USPATFULL  
 TITLE: Methods for remodeling neuronal and cardiovascular pathways  
 INVENTOR(S): Adams, Michael A., Kingston, CANADA  
 Heaton, Jeremy P.W., Gananoque, CANADA  
 PATENT ASSIGNEE(S): Cellegy Pharmaceuticals, Inc., South San Francisco, CA (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004234619	A1	20041125
APPLICATION INFO.:	US 2004-869755	A1	20040615 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2002-192281, filed on 9 Jul 2002, GRANTED, Pat. No. US 6787553 Continuation of Ser. No. US 2001-902787, filed on 12 Jul 2001, GRANTED, Pat.		



No. US 6458797 Continuation of Ser. No. US 1999-382749,  
filed on 25 Aug 1999, GRANTED, Pat. No. US 6284763

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1998-98178P	19980826 (60)	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834		
NUMBER OF CLAIMS:	23		
EXEMPLARY CLAIM:	CLM-01-33		
NUMBER OF DRAWINGS:	6 Drawing Page(s)		
LINE COUNT:	983		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a method of administration of an agent which acts to remodel neuronal or vascular pathways for the long term management of sexual dysfunction in both males and females. In a preferred embodiment, the invention provides a method of ameliorating or reversing pathogenic vascular degradative modeling in the ilio-hypogastric-pudendal arterial bed and genitalia comprising administering to a human patient in need of such treatment a therapeutically effective amount of an anti-pressor agent. The anti-pressor agent comprises one or more compounds selected from the therapeutic classes of direct vasodilators such as hydralazine and NO donors, ACE inhibitors, angiotensin-II receptor antagonists,  $\alpha$ .sub.1-adrenergic receptor antagonists,  $\beta$ -adrenergic receptor antagonists, calcium channel blockers, and phosphodiesterase inhibitors. The anti-pressor agent may be co-administered with a diuretic compound, and is administered either chronically at low dose, or for short periods of time at doses higher than are typically used for the treatment of hypertension. In certain embodiments of the method of the invention, the anti-pressor agent is co-administered with a diuretic agent and/or prostaglandin-E.sub.1.

PRAI US 1998-98178P 19980826 (60) <--

ST antipressor **cardiovascular** neuronal remodeling sexual dysfunction; diuretic antipressor **cardiovascular** neuronal remodeling sexual dysfunction; prostaglandin antipressor **cardiovascular** neuronal remodeling sexual dysfunction

IT Angiotensin receptors  
(AT1, antagonists; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)

IT Antihypertensives

IT **Cardiovascular** agents

IT Diuretics

IT Nervous system agents

IT Reproductive tract

IT Vasodilators

(anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)

IT Ion **channel** blockers

(calcium; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)

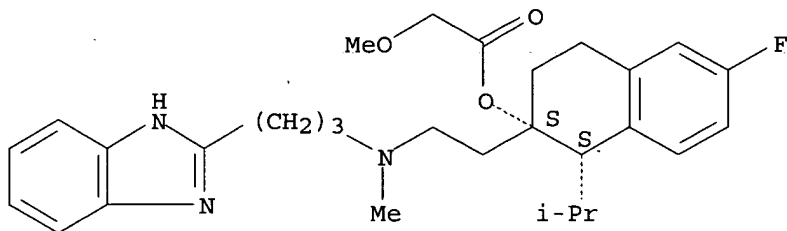
IT Sexual behavior

(disorder; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)

- IT Artery  
(ilio-hypogastric-pudendal arterial bed; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT Blood vessel  
(pathogenic vascular degradative modeling; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT Penis  
(penile vascular bed; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT Adrenoceptor antagonists  
( $\alpha$ 1-; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT Adrenoceptor antagonists  
( $\beta$ -; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT 9012-42-4, Adenyl cyclase 9054-75-5, Guanylyl cyclase  
(activators; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT 10102-43-9, Nitric oxide, biological studies  
(and NO donors; anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT 390-28-3, Methoxamine 11000-17-2, Vasopressin 11128-99-7, Angiotensin II  
(anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)
- IT 50-60-2, Phentolamine 52-53-9, Verapamil 55-63-0, Glyceryl trinitrate 59-96-1, Phenoxybenzamine 78-11-5, Pentaerythritol tetranitrate 86-54-4, Hydralazine 87-33-2, Isosorbide dinitrate 745-65-3, Prostaglandin E1 835-31-4, Naphazoline 4205-90-7, Clonidine 14402-89-2, Sodium nitroprusside 16051-77-7, Isosorbide 5-mononitrate 19216-56-9, Prazosin 21829-25-4, Nifedipine 25717-80-0, Molsidomine 26844-12-2, Indoramin 33876-97-0, 3-Morpholinomorpholine 34661-75-1, Urapidil 35795-16-5, Trimazosin 36894-69-6 42399-41-7, Diltiazem 42794-76-3, Midodrine 53054-07-2 55985-32-5, Nicardipine 57564-91-7, S-Nitrosoglutathione 60719-84-8, Amrinone 62571-86-2, Captopril 63590-64-7, Terazosin 64706-54-3, Bepridil 66085-59-4, Nimodipine 66575-29-9, Forskolin 66711-21-5, Apraclonidine 72822-12-9, Dapiprazole 72956-09-3, Carvedilol 74191-85-8, Doxazosin 74258-86-9, Alacepril 75847-73-3, Enalapril 76547-98-3, Lisinopril 79032-48-7, S-Nitroso-N-acetylpenicillamine 80755-51-7, Bunazosin 81403-80-7, Alfuzosin 82834-16-0, Perindopril 82924-03-6, Pentopril 83435-66-9, Delapril 83647-97-6, Spirapril 85441-61-8, Quinapril 85856-54-8, Moveltipril 86541-75-5, Benazepril 87333-19-5, Ramipril 87679-37-6, Trandolapril 88768-40-5, Cilazapril 89371-37-9, Imidapril 98048-97-6, Fosinopril 103775-10-6, Moexipril 103890-78-4, Lacidipine 106133-20-4, Tamsulosin 109214-55-3, Libenzapril 111223-26-8, Ceronapril 111902-57-9, Temocapril 114798-26-4, Losartan 116644-53-2, Mibefradil 133040-01-4, Eprosartan 137862-53-4, Valsartan 138402-11-6, Irbesartan 139755-83-2, Sildenafil 170632-47-0, YC-1  
(anti-pressor agents and methods for remodeling neuronal and **cardiovascular** pathways for long term management of sexual dysfunction)

dysfunction)  
 IT 9015-82-1 9025-82-5, Phosphodiesterase  
 (inhibitors; anti-pressor agents and methods for remodeling neuronal  
 and **cardiovascular** pathways for long term management of  
 sexual dysfunction)  
 IT 116644-53-2, Mibefradil  
 (anti-pressor agents and methods for remodeling neuronal and  
**cardiovascular** pathways for long term management of sexual  
 dysfunction)  
 RN 116644-53-2 USPATFULL  
 CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-  
 yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-  
 methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 60 OF 198 USPATFULL on STN  
 ACCESSION NUMBER: 2004:144459 USPATFULL  
 TITLE: Ion channel assay methods  
 INVENTOR(S): Maher, Michael P., San Diego, CA, UNITED STATES  
 Gonzalez, Jesus E., III, San Diego, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004110123	A1	20040610
APPLICATION INFO.:	US 2003-620312	A1	20030714 (10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2001-804457, filed on 12 Mar 2001, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-217671P	20000710 (60) <--
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	KNOBBE MARTENS OLSON & BEAR LLP, 2040 MAIN STREET, FOURTEENTH FLOOR, IRVINE, CA, 92614	
NUMBER OF CLAIMS:	10	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	46 Drawing Page(s)	
LINE COUNT:	5090	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

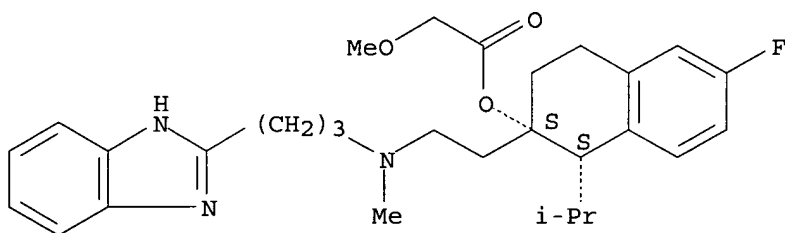
AB A method of characterizing the biological activity of a candidate compound may include exposing cells to the candidate compound, and then exposing the cells to a repetitive application of electric fields so as to set the transmembrane potential to a level corresponding to a pre-selected voltage dependent state of a target ion channel.

PRAI US 2000-217671P 20000710 (60) <--

ST ion channel assay elec field transmembrane potential; **calcium**  
**channel** elec stimulation FRET probe

- IT **Calcium channel**  
(L-type; ion channel assay methods using repetitive application of elec. fields to set transmembrane potential)
- IT Ion **channel** blockers  
(**calcium**, L-type; ion channel assay methods using repetitive application of elec. fields to set transmembrane potential)
- IT Muscle  
(**cardiac**, cells of; ion channel assay methods using repetitive application of elec. fields to set transmembrane potential)
- IT **Calcium channel**
- IT Chloride channel
- IT Potassium channel  
(ion **channel** assay methods using repetitive application of elec. fields to set transmembrane potential)
- IT **Calcium channel**
- IT Sodium channel  
(voltage-gated; ion channel assay methods using repetitive application of elec. fields to set transmembrane potential)
- IT 50-48-6, Amitriptyline 52-53-9, Verapamil 57-41-0, Phenytoin 66-40-0, Tetraethylammonium 85-79-0, Dibucaine 91-64-5, Coumarin 94-24-6, Tetracaine 137-58-6, Lidocaine 146-48-5, Yohimbine 404-86-4, Capsaicin 2609-46-3, Amiloride 4368-28-9, Tetrodotoxin 10361-37-2, Barium chloride, biological studies 21829-25-4 31828-71-4, Mexiletine 35523-89-8, Saxitoxin 38396-39-3, Bupivacaine 47623-98-3, DiSBAC2(3) 66085-59-4, Nimodipine 68844-77-9, Astemizole 84057-84-1, Lamotrigine **116644-53-2**, Mibefradil 169970-60-9 393782-57-5, CC2-DMPE  
(ion channel assay methods using repetitive application of elec. fields to set transmembrane potential)
- IT **116644-53-2**, Mibefradil  
(ion channel assay methods using repetitive application of elec. fields to set transmembrane potential)
- RN 116644-53-2 USPATFULL
- CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 61 OF 198 USPATFULL on STN  
 ACCESSION NUMBER: 2004:138678 USPATFULL  
 TITLE: Methods of treating vascular diseases characterized by nitric oxide insufficiency  
 INVENTOR(S): Loscalzo, Joseph, Dover, MA, UNITED STATES  
 Vita, Joseph A., Hingham, MA, UNITED STATES  
 Loberg, Michael D., Boston, MA, UNITED STATES  
 Worcel, Manuel, Boston, MA, UNITED STATES

NUMBER KIND DATE

PATENT INFORMATION: US 2004105850 A1 20040603  
 APPLICATION INFO.: US 2003-692724 A1 20031027 (10)  
 RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2003-679257, filed  
 on 7 Oct 2003, PENDING Continuation of Ser. No. US  
 2000-697317, filed on 27 Oct 2000, GRANTED, Pat. No. US  
 6635273

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-179020P	20000131 (60)	<--
	US 1999-162230P	19991029 (60)	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	EDWARD D GRIEFF, HALE & DORR LLP, 1455 PENNSYLVANIA AVE, NW, WASHINGTON, DC, 20004		
NUMBER OF CLAIMS:	36		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	3 Drawing Page(s)		
LINE COUNT:	2031		
CAS INDEXING IS AVAILABLE FOR THIS PATENT.			
AB	The invention provides methods of treating and/or preventing vascular diseases characterized by nitric oxide insufficiency by administering a therapeutically effective amount of at least one nitrosated angiotensin-converting enzyme inhibitor, nitrosated beta-adrenergic blocker, nitrosated cholesterol reducer, nitrosated calcium channel blocker, nitrosated endothelin antagonist, nitrosated angiotensin II receptor antagonist, nitrosated renin inhibitor, and optionally at least one compound used to treat cardiovascular diseases and/or at least one antioxidant, or a pharmaceutically acceptable salt thereof, and/or at least one compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase. The antioxidant may preferably be a hydralazine compound or a pharmaceutically acceptable salt thereof. The compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase may preferably be isosorbide dinitrate and/or isosorbide mononitrate. The vascular diseases characterized by nitric oxide insufficiency include a cardiovascular disease and a disease resulting from oxidative stress.		
PI	US 2004105850	A1 20040603	
RLI	Continuation-in-part of Ser. No. US 2003-679257, filed on 7 Oct 2003, PENDING Continuation of Ser. No. US 2000-697317, filed on 27 Oct 2000, GRANTED, Pat. No. US 6635273		
PRAI	US 2000-179020P	20000131 (60)	<--
PRAI	US 1999-162230P	19991029 (60)	<--
ST	nitrosated compd treatment vascular disease nitric oxide insufficiency; hypertension nitric oxide insufficiency human group		
IT	Heart, disease (angina pectoris, Prinzmetal, treatment of; nitrosated compds. in methods of treating vascular diseases characterized by nitric oxide insufficiency)		
IT	Heart, disease (angina pectoris, treatment of; nitrosated compds. in methods of treating vascular diseases characterized by nitric oxide insufficiency)		
IT	Heart, disease (angina pectoris, unstable, treatment of; nitrosated compds.)		

- in methods of treating vascular diseases characterized by nitric oxide insufficiency)
- IT Ion channel blockers  
(calcium, nitrosated; nitrosated compds. in methods of treating vascular diseases characterized by nitric oxide insufficiency)
- IT Ischemia  
(cardiac, microvascular, treatment of; nitrosated compds. in methods of treating vascular diseases characterized by nitric oxide insufficiency)
- IT Edema
- IT Ischemia  
(cardiac, treatment of; nitrosated compds. in methods of treating vascular diseases characterized by nitric oxide insufficiency)
- IT Pregnancy  
(disorder, hypertension, treatment of; nitrosated compds. in methods of treating vascular diseases characterized by nitric oxide insufficiency)
- IT Heart, disease  
(edema, treatment of; nitrosated compds. in methods of treating vascular diseases characterized by nitric oxide insufficiency)
- IT Kidney, disease  
(failure, chronic, irreversible, hypertension-dependent, treatment of; nitrosated compds. in methods of treating vascular diseases characterized by nitric oxide insufficiency)
- IT Heart, disease  
(failure, treatment of; nitrosated compds. in methods of treating vascular diseases characterized by nitric oxide insufficiency)
- IT 52-53-9D, Verapamil, nitrosated compds. 54-31-9D, Furosemide, nitrosated compds. 54-80-8D, Pronethalol, nitrosated compds. 55-73-2D, Bethanidine, nitrosated compds. 83-46-5D,  $\beta$ -Sitosterol, nitrosated compds. 525-66-6D, Propranolol, nitrosated compds. 2933-94-0D, Toliprolol, nitrosated compds. 3930-20-9D, Sotalol, nitrosated compds. 5741-22-0D, Moprolol, nitrosated compds. 6452-71-7D, Oxprenolol, nitrosated compds. 6673-35-4D, Practolol, nitrosated compds. 7413-36-7D, Nifenalol, nitrosated compds. 9004-54-0D, Dextran, crosslinked, nitrosated alkylaminoalkyl derivs., biological studies 9028-35-7D, HMG-CoA reductase, nitrosated compds. 11041-12-6D, Cholestyramine, nitrosated compds. 13523-86-9D, Pindolol, nitrosated compds. 13655-52-2D, Alprenolol, nitrosated compds. 14417-88-0D, Melinamide, nitrosated compds. 14556-46-8D, Bupranolol, nitrosated compds. 21829-25-4D, Nifedipine, nitrosated compds. 22664-55-7D, Metipranolol, nitrosated compds. 23694-81-7D, Mepindolol, nitrosated compds. 26839-75-8D, Timolol, nitrosated compds. 29122-68-7D, Atenolol, nitrosated compds. 30187-90-7D, Xibenolol, nitrosated compds. 34273-10-4D, Saralasin, nitrosated compds. 34661-75-1D, Urapidil, nitrosated compds. 34915-68-9D, Bunitrolol, nitrosated compds. 34919-98-7D, Cetamolol, nitrosated compds. 36894-69-6D, Labetalol, nitrosated compds. 37517-30-9D, Acebutolol, nitrosated compds. 38363-40-5D, Penbutolol, nitrosated compds. 39562-70-4D, Nitrendipine, nitrosated compds. 42200-33-9D, Nadolol, nitrosated compds. 42399-41-7D, Diltiazem, nitrosated compds. 50925-79-6D, Colestipol, nitrosated compds. 51384-51-1D, Metoprolol, nitrosated compds. 51781-06-7D, Carteolol, nitrosated compds. 53684-49-4D, Bufetolol, nitrosated compds. 54063-51-3D, Nadoxolol, nitrosated compds. 54340-62-4D, Bufuralol, nitrosated compds. 55985-32-5D, Nicardipine, nitrosated compds. 56980-93-9D, Celiprolol, nitrosated compds. 57460-41-0D, Talinolol, nitrosated compds. 57775-29-8D, Carazolol, nitrosated compds. 58409-59-9D, Bucumolol, nitrosated compds. 58930-32-8D, Butofilolol, nitrosated compds. 59170-23-9D, Bevantolol, nitrosated compds. 60607-68-3D, Indenolol,

nitrosated compds. 62571-86-2D, Captopril, nitrosated compds.  
 62658-63-3D, Bopindolol, nitrosated compds. 63659-18-7D, Betaxolol,  
 nitrosated compds. 63675-72-9D, Nisoldipine, nitrosated compds.  
 66264-77-5D, Sulfinalol, nitrosated compds. 66564-16-7D, Ciclosidomine,  
 nitrosated compds. 66722-44-9D, Bisoprolol, nitrosated compds.  
 68377-92-4D, Arotinolol, nitrosated compds. 72509-76-3D, Felodipine,  
 nitrosated compds. 72956-09-3D, Carvedilol, nitrosated compds.  
 74258-86-9D, Alacepril, nitrosated compds. 75330-75-5D, Lovastatin,  
 nitrosated compds. 75530-68-6D, Nilvadipine, nitrosated compds.  
 75659-07-3D, Dilevalol, nitrosated compds. 75695-93-1D, Isradipine,  
 nitrosated compds. 75847-73-3D, Enalapril, nitrosated compds.  
 76420-72-9D, Enalaprilat, nitrosated compds. 76547-98-3D, Lisinopril,  
 nitrosated compds. 79902-63-9D, Simvastatin, nitrosated compds.  
 80830-42-8D, Rentiapril, nitrosated compds. 81093-37-0D, Pravastatin,  
 nitrosated compds. 81147-92-4D, Esmolol, nitrosated compds.  
 81486-22-8D, Nipradilol, nitrosated compds. 81872-10-8D, Zofenopril,  
 nitrosated compds. 82834-16-0D, Perindopril, nitrosated compds.  
 82924-03-6D, Pentopril, nitrosated compds. 83435-66-9D, Delapril,  
 nitrosated compds. 83647-97-6D, Spirapril, nitrosated compds.  
 83688-84-0D, Tertatolol, nitrosated compds. 85136-71-6D, Tilisolol,  
 nitrosated compds. 85320-68-9D, Amosulalol, nitrosated compds.  
 85441-61-8D, Quinapril, nitrosated compds. 85856-54-8D, Moveltipril,  
 nitrosated compds. 86541-75-5D, Benazepril, nitrosated compds.  
 86780-90-7D, Aranidipine, nitrosated compds. 86880-51-5D, Epanolol,  
 nitrosated compds. 87333-19-5D, Ramipril, nitrosated compds.  
 87679-37-6D, Trandolapril, nitrosated compds. 88150-42-9D, Amlodipine,  
 nitrosated compds. 88768-40-5D, Cilazapril, nitrosated compds.  
 89226-50-6D, Manidipine, nitrosated compds. 89371-37-9D, Imidapril,  
 nitrosated compds. 93957-54-1D, Fluvastatin, nitrosated compds.  
 96125-53-0D, Clentiazem, nitrosated compds. 98048-97-6D, Fosinopril,  
 nitrosated compds. 100427-26-7D, Lercanidipine, nitrosated compds.  
 103890-78-4D, Lacidipine, nitrosated compds. 104713-75-9D, Barnidipine,  
 nitrosated compds. 105979-17-7D, Benidipine, nitrosated compds.  
 111011-63-3D, Efonidipine, nitrosated compds. 111223-26-8D, Ceronapril,  
 nitrosated compds. 111902-57-9D, Temocapril, nitrosated compds.  
 113082-98-7D, Enalkiren, nitrosated compds. 114432-13-2D, Fantofarone,  
 nitrosated compds. 114798-26-4D, Losartan, nitrosated compds.  
 115404-79-0D, ES 1005, nitrosated compds. 116476-13-2D, Semotiadil,  
 nitrosated compds. **116644-53-2D**, Mibefradil, nitrosated compds.  
 118457-14-0D, Nebivolol, nitrosated compds. 119625-78-4D, CP 80794,  
 nitrosated compds. 122224-84-4D, A 65317, nitrosated compds.  
 126222-34-2D, RO 42-5892, nitrosated compds. 129445-88-1D, ES 8891,  
 nitrosated compds. 132203-70-4D, Cilnidipine, nitrosated compds.  
 133040-01-4D, Eprosartan, nitrosated compds. 134523-00-5D,  
 Atorvastatin, nitrosated compds. 136553-81-6D, BQ 123, nitrosated  
 compds. 137862-53-4D, Valsartan, nitrosated compds. 138402-11-6D,  
 Irbesartan, nitrosated compds. 145599-86-6D, Cerivastatin, nitrosated  
 compds. 147536-97-8D, Bosentan, nitrosated compds. 185036-49-1D, SQ  
 28608, nitrosated compds. 695226-77-8D, SQ 34017, nitrosated compds.

(nitrosated compds. in methods of treating vascular diseases  
 characterized by nitric oxide insufficiency)

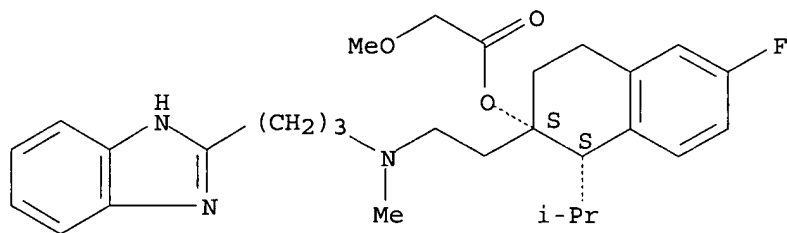
IT **116644-53-2D**, Mibefradil, nitrosated compds.

(nitrosated compds. in methods of treating vascular diseases  
 characterized by nitric oxide insufficiency)

RN 116644-53-2 USPATFULL

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 62 OF 198    USPATFULL on STN  
 ACCESSION NUMBER:    2004:83263    USPATFULL  
 TITLE:    Combination therapy using antihypertensive agents and endothelin antagonists  
 INVENTOR(S) :    Adams, Michael A., Kingston, CANADA  
                   Hale, Taben M., Kingston, CANADA  
                   Heaton, Jeremy P.W., Gananoque, CANADA  
 PATENT ASSIGNEE(S) :    Queen's University at Kingston, Kingston, CANADA  
                           (non-U.S. corporation)  
                           Callegy Pharmaceuticals, Inc., South San Francisco, CA  
                           (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004063719	A1	20040401
APPLICATION INFO.:	US 2003-429197	A1	20030502 (10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2002-192281, filed on 9 Jul 2002, PENDING Continuation of Ser. No. US 2001-902787, filed on 12 Jul 2001, GRANTED, Pat. No. US 6458797 Continuation of Ser. No. US 1999-382749, filed on 25 Aug 1999, GRANTED, Pat. No. US 6284763		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-98178P	19980826 (60)
	US 2002-377917P	20020502 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834	
NUMBER OF CLAIMS:	47	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	13 Drawing Page(s)	
LINE COUNT:	1587	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB    The present invention provides a method for a more efficacious treatment of a vascular condition through the administration of a therapeutically effective amount of a combination of an anti-pressor agent, an endothelin antagonist, and a sex hormone for repetitive cycles of on/off-treatment. In one embodiment, the invention provides a method for the prevention of tolerance induced by an anti-pressor agent via the inclusion of an endothelin antagonist in a combination therapy approach to remodel vascular structure and treat vascular conditions associated with a male or female sexual dysfunction, atherosclerosis, renal failure, hypertension, congestive heart failure, diabetic nephropathy, and diabetic neuropathy. The anti-pressor agent comprises one or more compounds such as prostaglandin-E.sub.1, an ACE inhibitor, an angiotensin-II receptor antagonist, an  $\alpha$ .sub.1-adrenergic receptor



antagonist, a  $\beta$ -adrenergic receptor antagonist, a calcium channel blocker, an activator of guanylyl cyclase or adenylyl cyclase, a phosphodiesterase inhibitor, and hydralazine. The endothelin antagonist comprises one or more compounds such as a peptidal endothelin antagonist, a non-peptidal endothelin antagonist, and an inhibitor of endothelin converting enzyme. Such a combination therapy approach enhances the efficacy of the anti-pressor agent and enables an increase in the frequency and duration of anti-pressor administrations for the long term treatment of vascular conditions.

PRAI US 1998-98178P 19980826 (60) <--

IT Ion channel blockers  
(calcium, as anti-pressor agent; combination therapy using antihypertensive agents and endothelin antagonists for vascular conditions associated with a male or female sexual dysfunction)

IT Antidiabetic agents

IT Atherosclerosis

IT Blood vessel, disease

IT Diabetes mellitus

IT Human

IT Hypertension  
(combination therapy using antihypertensive agents and endothelin antagonists for vascular conditions associated with a male or female sexual dysfunction)

IT Heart, disease

IT Kidney, disease  
(failure; combination therapy using antihypertensive agents and endothelin antagonists for vascular conditions associated with a male or female sexual dysfunction)

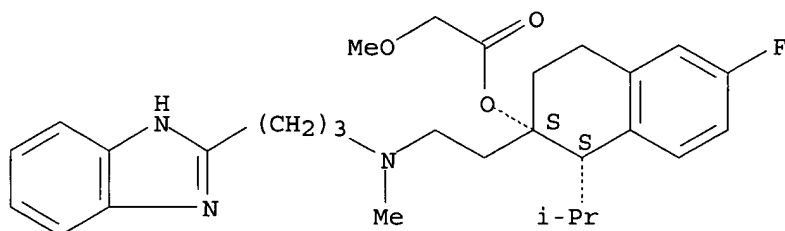
IT 50-60-2, Phentolamine 52-53-9, Verapamil 59-96-1, Phenoxybenzamine 835-31-4, Naphazoline 4205-90-7, Clonidine 19216-56-9, Prazosin 21829-25-4, Nifedipine 26844-12-2, Indoramin 34661-75-1, Urapidil 35795-16-5, Trimazosin 36357-77-4, Phosphoramidon 36894-69-6, Labetalol 42399-41-7, Diltiazem 42794-76-3, Midodrine 55985-32-5, Nicardipine 60719-84-8, Amrinone 62571-86-2, Captopril 63590-64-7, Terazosin 64706-54-3, Bepridil 66085-59-4, Nimodipine 66575-29-9, Forskolin 66711-21-5, Apraclonidine 72822-12-9, Dapiprazole 72956-09-3, Carvedilol 74191-85-8, Doxazosin 74258-86-9, Alacepril 75847-73-3, Enalapril 76547-98-3, Lisinopril 80755-51-7, Bunazosin 81403-80-7, Alfuzosin 82834-16-0, Perindopril 82924-03-6, Pentopril 83435-66-9, Delapril 83647-97-6, Spirapril 85441-61-8, Quinapril 85856-54-8, Moveltipril 86541-75-5, Benazepril 87333-19-5, Ramipril 87679-37-6, Trandolapril 88768-40-5, Cilazapril 89371-37-9, Imidapril 98048-97-6, Fosinopril 103775-10-6, Moexipril 103890-78-4, Lacidipine 106133-20-4, Tamsulosin 109214-55-3, Libenzapril 111223-26-8, Ceronapril 111902-57-9, Temocapril 114798-26-4, Losartan 116644-53-2, Mibefradil 133040-01-4, Eprosartan 137862-53-4, Valsartan 138238-81-0, Endothelin converting enzyme. 138402-11-6, Irbesartan 139755-83-2, Sildenafil 147536-97-8, Bosentan 151039-37-1, PD145065 170632-47-0, YC 1  
(combination therapy using antihypertensive agents and endothelin antagonists for vascular conditions associated with a male or female sexual dysfunction)

IT 116644-53-2, Mibefradil  
(combination therapy using antihypertensive agents and endothelin antagonists for vascular conditions associated with a male or female sexual dysfunction)

RN 116644-53-2 USPATFULL

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 63 OF 198 USPATFULL on STN  
 ACCESSION NUMBER: 2004:45243 USPATFULL  
 TITLE: Materials and methods for the treatment of hypertension and angina  
 INVENTOR(S): Druzgala, Pascal, Santa Rosa, CA, UNITED STATES  
 Milner, Peter G., Los Altos Hills, CA, UNITED STATES  
 Pfister, Jurg, Los Altos, CA, UNITED STATES  
 Zhang, Xiaoming, Campbell, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004034237	A1	20040219
APPLICATION INFO.:	US 2003-643699	A1	20030818 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2002-269139, filed on 10 Oct 2002, GRANTED, Pat. No. US 6608097		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-328588P	20011010 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	SALIWANCHIK LLOYD & SALIWANCHIK, A PROFESSIONAL ASSOCIATION, 2421 N.W. 41ST STREET, SUITE A-1, GAINESVILLE, FL, 326066669	
NUMBER OF CLAIMS:	33	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	12 Drawing Page(s)	
LINE COUNT:	793	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The subject invention provides useful and novel calcium channel blockers based upon mibefradil. The subject invention also provides methods for synthesizing the compounds of the invention. The invention also provides methods for the control or prevention of hypertension, angina pectoris, ischemia, arrhythmias, and cardiac insufficiency in a patient by administering a compound, or composition, of the invention to an individual in need of such treatment.

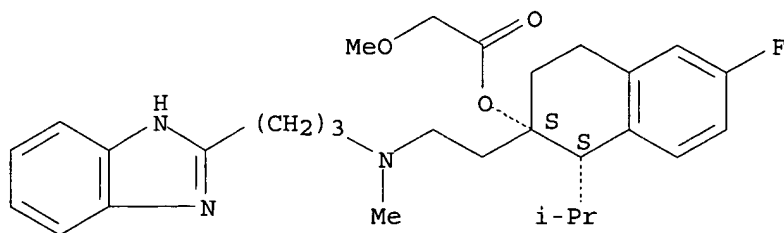
PRAI US 2001-328588P 20011010 (60) <--

ST mibefradil deriv **calcium channel** blocker therapeutic;  
**hypertension** mibefradil deriv **calcium channel**  
 blocker; **angina** mibefradil deriv **calcium**  
**channel** blocker; **ischemia** mibefradil deriv  
**calcium channel** blocker; **arrhythmia**  
 mibefradil deriv **calcium channel** blocker;  
**cardiac** insufficiency mibefradil deriv **calcium**  
**channel** blocker

IT **Heart**, disease

- (angina pectoris; mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)
- IT Heart, disease  
(arrhythmia; mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)
- IT Ion channel blockers  
(calcium; mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)
- IT Heart, disease  
(failure; mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)
- IT Liver  
(liver function test; mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)
- IT Enzymes, biological studies  
(metabolic, non-oxidative; mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)
- IT Drug interactions  
(metabolic; mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)
- IT Anti-ischemic agents
- IT Antiarrhythmics
- IT Antihypertensives
- IT Cardiovascular agents
- IT Drug delivery systems
- IT Drug metabolism
- IT Human
- IT Hypertension
- IT Ischemia
- IT Pharmacokinetics  
(mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)
- IT 9027-41-2, Hydrolase 9035-51-2, Cytochrome P 450, biological studies  
(mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)
- IT 116644-53-2D, Mibefradil, derivs.  
(mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)
- IT 116644-53-2D, Mibefradil, derivs.  
(mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)
- RN 116644-53-2 USPATFULL
- CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 64 OF 198    USPATFULL on STN  
 ACCESSION NUMBER:        2003:283148    USPATFULL  
 TITLE:                    Combination therapy  
 INVENTOR(S):             Scott, Robert Andrew Donald, Riverside, CT, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003199492	A1	20031023
APPLICATION INFO.:	US 2003-442285	A1	20030519 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2001-45329, filed on 23 Oct 2001, ABANDONED		
	Continuation of Ser. No. US 2000-513887, filed on 25 Feb 2000, ABANDONED		
	Continuation of Ser. No. WO 1998-IB1230, filed on 11 Aug 1998, UNKNOWN		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-57276P	19970829 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	CONNOLLY BOVE LODGE & HUTZ, LLP, 1220 N MARKET STREET, P O BOX 2207, WILMINGTON, DE, 19899	
NUMBER OF CLAIMS:	67	
EXEMPLARY CLAIM:	1	
LINE COUNT:	1773	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB    This invention relates to pharmaceutical combinations of atorvastatin or a pharmaceutically acceptable salt thereof and antihypertensive agents, kits containing such combinations and methods of using such combinations to treat subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and to treat subjects presenting with symptoms of cardiac risk, including humans. This invention also relates to additive and synergistic combinations of atorvastatin or a pharmaceutically acceptable salt thereof and antihypertensive agents whereby those synergistic combinations are useful in treating subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and those subjects presenting with symptoms of cardiac risk, including humans.

PRAI    US 1997-57276P        19970829 (60)        <--  
 IT    Ion **channel** blockers  
       (**calcium**; combination therapy comprising atorvastatin and antihypertensive agent)  
 IT    **Heart**, disease  
       (failure; combination therapy comprising atorvastatin and antihypertensive agent for **cardiac** risk management)  
 IT    52-53-9, Verapamil    73-48-3, Bendroflumethiazide    2609-46-3, Amiloride  
       19216-56-9, Prazosin    21829-25-4, Nifedipine    35795-16-5, Trimazosin

39562-70-4, Nitrendipine 42399-41-7, Diltiazem 55985-32-5,  
 Nicardipine 62571-86-2, Captopril 63675-72-9, Nisoldipine  
 66085-59-4, Nimodipine 72509-76-3, Felodipine 72956-09-3, Carvedilol  
 74191-85-8, Doxazosin 75695-93-1, Isradipine 75847-73-3, Enalapril  
 76547-98-3, Lisinopril 82834-16-0, Perindopril 85441-61-8, Quinapril  
 86541-75-5, Benazepril 87679-37-6, Trandolapril 98048-97-6,  
 Fosinopril 103890-78-4, Lacidipine 114798-26-4, Losartan  
 116644-53-2, Mibefradil 134523-00-5, Atorvastatin  
 134523-03-8, Atorvastatin calcium 137862-53-4, Valsartan 138402-11-6,  
 Irbesartan

(combination therapy comprising atorvastatin and antihypertensive agent)

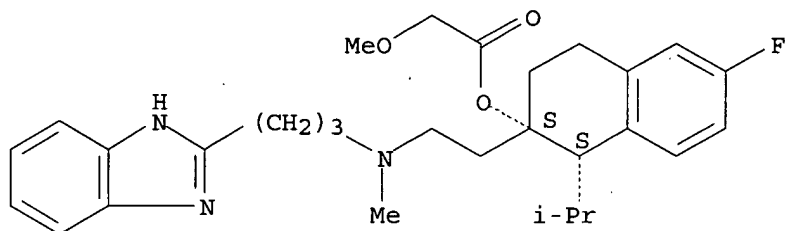
IT 116644-53-2, Mibefradil

(combination therapy comprising atorvastatin and antihypertensive agent)

RN 116644-53-2 USPATFULL

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 65 OF 198 USPATFULL on STN  
 ACCESSION NUMBER: 2003:181436 USPATFULL  
 TITLE: T-TYPE CALCIUM CHANNEL  
 INVENTOR(S): LI, MING, MOBILE, AL, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003125269	A1	20030703
APPLICATION INFO.:	US 1999-383894	A1	19990826 (9) <--

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-98004P	19980826 (60) <--
	US 1999-117399P	19990127 (60) <--
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	SUSAN J BRAMAN ESQ, BRAMAN & ROGALSKYJ LLP, P O BOX 352, CANANDAIGUA, NY, 144240352	
NUMBER OF CLAIMS:	60	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	15 Drawing Page(s)	
LINE COUNT:	3290	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to isolated nucleic acid molecules encoding pancreatic T-type calcium channels. Expression vectors and host cells comprising the nucleic acid molecules are also provided, as well as methods for increasing or decreasing the expression of pancreatic

T-type calcium channel in host cells. The invention further provides a method of screening a substance for the ability of the substance to modify T-type calcium channel function, and a method for isolating other pancreatic T-type calcium channel molecules. DNA oligomers capable of hybridizing to the nucleic acid molecule encoding the pancreatic T-type calcium channel are provided, which can be used to detect pancreatic T-type calcium channel in a sample. An isolated pancreatic T-type calcium channel protein is also provided. Antibodies specific for the protein, and fragments thereof, are provided, as are compositions comprising the protein and a compatible carrier. The subject invention further provides a method of modifying insulin secretion by pancreatic beta cells, a method of treating type II diabetes in a subject, a method of modifying basal calcium levels in cells, a method of modifying the action potential of L type calcium channels in cells, a method of modifying pancreatic beta cell death, a method of modifying pancreatic beta cell proliferation, and a method of modifying calcium influx through L type calcium channels in cells.

AI	US 1999-383894	A1	19990826 (9)	<--
PRAI	US 1998-98004P		19980826 (60)	<--
PRAI	US 1999-117399P		19990127 (60)	<--

ST rat antisense Ttype **calcium channel** diabetes therapy probe sequence

IT Nucleic acid hybridization  
(DNA-DNA; sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT Primers (nucleic acid)

IT Primers (nucleic acid)  
(DNA; sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT **Calcium channel**  
(L-type, methods for modification of function of; sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT **Calcium channel**  
(T-type; sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT Translation, genetic  
(antisense-DNA mediated blockage of; sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT Virus vectors  
(applications for; sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT Antibodies  
(complexes, detection of; sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT Antibodies  
(labeled; sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT Antibodies  
(monoclonal; sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT Diabetes mellitus  
(non-insulin-dependent; sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT DNA

IT DNA

(primer; sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT Cell death

IT Genetic vectors

IT Genomic library

IT Pancreas

IT Protein sequences

IT cDNA library

IT cDNA sequences  
(sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT Antibodies  
(sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT Antisense oligonucleotides

IT Probes (nucleic acid)  
(sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT Antisense DNA

IT Ribozymes  
(sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT Pancreatic islet of Langerhans  
( $\beta$ -cell; sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT 261889-03-6, T-type **calcium channel** (rat)  
(amino acid sequence; sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT 261889-04-7, DNA (rat T-type **calcium channel** cDNA)  
(nucleotide sequence; sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT 14127-61-8,  $\text{Ca}^{2+}$ , biological studies  
(relationship with NIDDM; sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT 116644-53-2, Mibefradil  
(sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT 261893-14-5, 1: PN: WO0015845 PAGE: 19 unclaimed DNA 261893-17-8, 5: PN: WO0015845 PAGE: 19 unclaimed DNA 261893-18-9, 6: PN: WO0015845 PAGE: 19 unclaimed DNA 261893-19-0, 8: PN: WO0015845 PAGE: 19 unclaimed DNA  
(unclaimed nucleotide sequence; sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

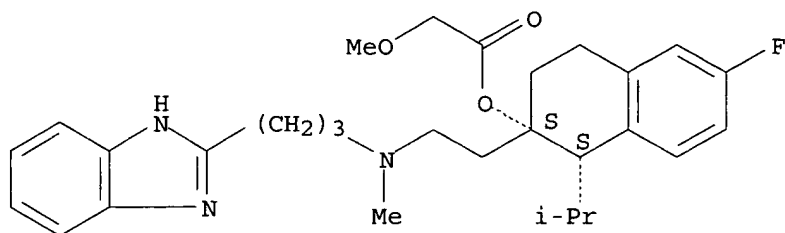
IT 261771-62-4 261893-15-6 261893-16-7  
(unclaimed sequence; sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

IT 116644-53-2, Mibefradil  
(sequence and therapeutic applications for rat pancreatic T-type **calcium channel** as it relates to diabetes)

RN 116644-53-2 USPATFULL

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 66 OF 198    USPATFULL on STN  
 ACCESSION NUMBER:    2003:127584    USPATFULL  
 TITLE:    Modulation  
 INVENTOR(S):    Wolfart, Jakob, Sceaux, FRANCE  
                   Roeper, Jochen, Marburg, GERMANY, FEDERAL REPUBLIC OF

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003087799	A1	20030508
APPLICATION INFO.:	US 2002-216128	A1	20020809 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	GB 2001-26781	20011107
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	FROMMER LAWRENCE & HAUG, 745 FIFTH AVENUE- 10TH FL., NEW YORK, NY, 10151	
NUMBER OF CLAIMS:	52	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	5 Drawing Page(s)	
LINE COUNT:	5439	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB    A method of treatment is described. The method comprises administering to a subject in need of same an agent, wherein said agent is capable of causing a dopaminergic neuron to enter bursting mode and/or of preventing it from leaving bursting mode. In a preferred aspect, the said agent modulates: a T-type channel and/or an SK (preferably SK3) channel and/or the coupling of a T-type channel with an SK (preferably SK3) channel.

PRAI    GB 2001-26781    20011107    <--

ST    small conductance **calcium** activated potassium **channel** modulator therapeutic; T type **calcium channel** modulator therapeutic; Parkinson drug **calcium channel** potassium **channel** modulator; dopaminergic neuron bursting mode **calcium channel** potassium **channel** therapeutic

IT    Neurotransmission  
       (bursting; modulators of small-conductance, calcium-activated potassium (SK) channels and T-type **calcium channels**, and therapeutic use)

IT    Potassium **channel**  
       (**calcium**-activated; modulators of small-conductance, calcium-activated potassium (SK) channels and T-type **calcium channels**, and therapeutic use)

IT    Ion **channel** blockers  
       (**calcium**; modulators of small-conductance, calcium-activated potassium (SK) channels and T-type **calcium channels**, and therapeutic use)



IT Nervous system, disease  
(degeneration, diagnosis; modulators of small-conductance, calcium-activated potassium (SK) channels and T-type **calcium channels**, and therapeutic use)

IT Nerve  
(dopaminergic; modulators of small-conductance, calcium-activated potassium (SK) channels and T-type **calcium channels**, and therapeutic use)

IT Disease, animal  
(genetic; modulators of small-conductance, calcium-activated potassium (SK) channels and T-type **calcium channels**, and therapeutic use)

IT Brain  
(midbrain, dopaminergic system; modulators of small-conductance, calcium-activated potassium (SK) channels and T-type **calcium channels**, and therapeutic use)

IT Antiparkinsonian agents

IT Drug design

IT Drug screening

IT Nervous system agents

IT Parkinson's disease  
(modulators of small-conductance, calcium-activated potassium (SK) channels and T-type **calcium channels**, and therapeutic use)

IT **Calcium channel**  
(modulators of small-conductance, calcium-activated potassium (SK) channels and T-type **calcium channels**, and therapeutic use)

IT Diagnosis  
(neurodegenerative disorder; modulators of small-conductance, calcium-activated potassium (SK) channels and T-type **calcium channels**, and therapeutic use)

IT Ion channel blockers  
(potassium; modulators of small-conductance, calcium-activated potassium (SK) channels and T-type **calcium channels**, and therapeutic use)

IT 51-61-6, Dopamine, biological studies  
(modulators of small-conductance, calcium-activated potassium (SK) channels and T-type **calcium channels**, and therapeutic use)

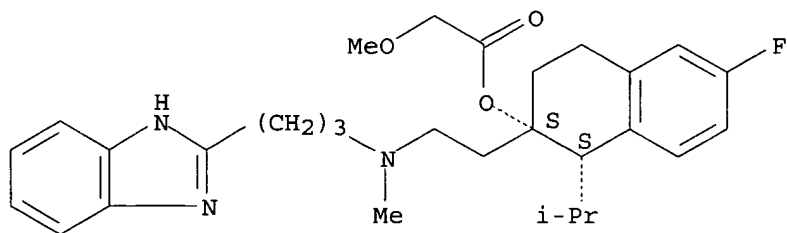
IT 7440-02-0, Nickel, biological studies 7440-48-4, Cobalt, biological studies 21829-25-4, Nifedipine 24345-16-2, Apamin 106375-28-4,  $\omega$ -Conotoxin G VIA **116644-53-2**, Mibefradil 156743-03-2, FTX-3.3 158484-42-5,  $\omega$ -Agatoxin TK  
(modulators of small-conductance, calcium-activated potassium (SK) channels and T-type **calcium channels**, and therapeutic use)

IT **116644-53-2**, Mibefradil  
(modulators of small-conductance, calcium-activated potassium (SK) channels and T-type **calcium channels**, and therapeutic use)

RN 116644-53-2 USPATFULL

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 67 OF 198    USPATFULL on STN  
 ACCESSION NUMBER:    2003:126768    USPATFULL  
 TITLE:    Method for the suppression of visceral pain by  
           regulating T type calcium channel  
 INVENTOR(S) :    Shin, Hee-Sup, Uiwang-si, KOREA, REPUBLIC OF  
                   Kim, Dae-Soo, Seoul, KOREA, REPUBLIC OF  
                   Kim, Chan-Ki, Seoul, KOREA, REPUBLIC OF

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003086980	A1	20030508
APPLICATION INFO.:	US 2002-284889	A1	20021031 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	KR 2001-68180	20011102
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Michael N. Mercanti, Roberts and Mercanti, L.L.P., Suite 203, 105 Lock Street, Newark, NJ, 07103	
NUMBER OF CLAIMS:	8	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	4 Drawing Page(s)	
LINE COUNT:	399	

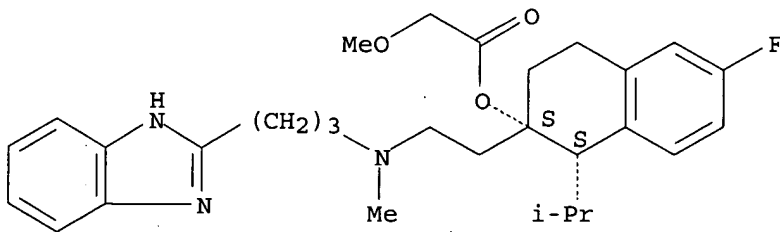
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB    The disclosure concerns a method for the suppression of visceral pain by regulating the T-type calcium channel; a visceral pain inhibitor that includes a T-type calcium channel inhibitor as an effective ingredient; and a method of screening a visceral pain inhibitor by investigating the suppression activity of T-type calcium channels. Particularly, the present invention relates to a method for the suppression of visceral pain by regulating an alpha 1G T-type calcium channel in the central nervous system and alpha 1H and alpha 1I T-type calcium channels in the peripheral nervous system; a visceral pain inhibitor that includes a T-type calcium channel inhibitor as an effective ingredient; and a method of screening a visceral pain inhibitor by investigating the suppression activity of T-type calcium channels. The method of the present invention can be effectively used to suppress visceral pain by regulating T-type calcium channel in a precise mechanism without any side effects.

PRAI    KR 2001-68180    20011102    <--  
 ST    visceral pain suppression T type **calcium channel**;  
       mibefradil analgesia visceral pain  
 IT    **Calcium channel**  
       (T-type,  $\alpha$  1G, regulation in central nervous system; suppression  
       of visceral pain by regulating T type **calcium channel**  
       )  
 IT    **Calcium channel**

- (T-type,  $\alpha$  1H, regulation in peripheral nervous system; suppression of visceral pain by regulating T type calcium channel)
- IT Calcium channel  
(T-type,  $\alpha$  1H, regulation in peripheral nervous system; suppression of visceral pain by regulating T type calcium channel)
- IT Calcium channel  
(T-type; suppression of visceral pain by regulating T type calcium channel)
- IT Ion channel blockers
- IT Ion channel openers  
(calcium; suppression of visceral pain by regulating T type calcium channel)
- IT Nervous system  
(central; suppression of visceral pain by regulating T type calcium channel)
- IT Viscera  
(disease, pain; suppression of visceral pain by regulating T type calcium channel)
- IT Nervous system  
(peripheral; suppression of visceral pain by regulating T type calcium channel)
- IT Analgesia
- IT Drug screening  
(suppression of visceral pain by regulating T type calcium channel)
- IT Disease, animal  
(visceral pain; suppression of visceral pain by regulating T type calcium channel)
- IT Pain  
(visceral; suppression of visceral pain by regulating T type calcium channel)
- IT 14701-22-5, Ni<sup>2+</sup>, biological studies 116644-53-2, Mibefradil  
(as T-type calcium channel inhibitor; suppression of visceral pain by regulating T type calcium channel)
- IT 116644-53-2, Mibefradil  
(as T-type calcium channel inhibitor; suppression of visceral pain by regulating T type calcium channel)
- RN 116644-53-2 USPATFULL
- CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 68 OF 198 USPATFULL on STN

ACCESSION NUMBER: 2003:99824 USPATFULL  
 TITLE: Jet propulsion boat  
 INVENTOR(S): Fuse, Tomohiro, Saitama, JAPAN

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003068933	A1	20030410
	US 6776675	B2	20040817
APPLICATION INFO.:	US 2002-216866	A1	20020813 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	JP 2001-283784	20010918
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	BIRCH STEWART KOLASCH & BIRCH, PO BOX 747, FALLS CHURCH, VA, 22040-0747	
NUMBER OF CLAIMS:	16	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	9 Drawing Page(s)	
LINE COUNT:	588	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB To provide a jet propulsion boat which can be efficiently propelled by disposing a steering nozzle closer to the bottom of the boat. A jet propulsion boat includes a jet propulsion apparatus driven by an engine at the stern. A jet nozzle for jetting water is provided at the rear portion of the jet propulsion apparatus. A steering nozzle is swingably supported by the jet nozzle so as to adjust the direction of a stream of water jetted from the jet nozzle. In the jet propulsion boat, an outlet side of the jet nozzle is covered with an inlet side of the steering nozzle and the vertical diameter D2 of the inlet of the steering nozzle is set to be smaller than the transverse diameter D1 of the inlet.

PI US 2003068933 A1 20030410  
 B2 20040817

PRAI JP 2001-283784 20010918 <--

IT Edema  
 (cardiac; synthesis of nitrosated and nitrosylated (hetero)cyclic phosphodiesterase inhibitors used in treatment of sexual dysfunction)

IT Calcium channel blockers

IT Dopamine agonists

IT Opioid antagonists

IT Potassium channel openers

IT Vasodilators

(combination pharmaceutical; synthesis of nitrosated and nitrosylated (hetero)cyclic phosphodiesterase inhibitors used in treatment of sexual dysfunction)

IT Heart, disease

(edema; synthesis of nitrosated and nitrosylated (hetero)cyclic phosphodiesterase inhibitors used in treatment of sexual dysfunction)

IT Heart, disease

(infarction; synthesis of nitrosated and nitrosylated (hetero)cyclic phosphodiesterase inhibitors used in treatment of sexual dysfunction)

IT Hypertension

(pulmonary; synthesis of nitrosated and nitrosylated (hetero)cyclic phosphodiesterase inhibitors used in treatment of sexual dysfunction)

IT 56-85-9, L-Glutamine, biological studies 58-32-2D, Dipyrindamole, nitroso derivs. 58-55-9D, Theophylline, nitroso derivs. 70-26-8, L-Ornithine 74-79-3, L-Arginine, biological studies 74-79-3D, L-Arginine, nitroso derivs. 156-86-5, L-Homoarginine 372-75-8,

(synthesis of nitrosated and nitrosylated (hetero)cyclic phosphodiesterase inhibitors used in treatment of sexual dysfunction)

(synthesis of nitrosated and nitrosylated (hetero)cyclic phosphodiesterase inhibitors used in treatment of sexual dysfunction)

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride (9CI) (CA INDEX NAME)

L103 ANSWER 69 OF 198    USPATFULL on STN  
ACCESSION NUMBER:        2003:72014    USPATFULL  
TITLE:                    Combination of aldose reductase inhibitors and  
                              angiotensin-II antagonists for the treatment of

INVENTOR(S): diabetic nephropathy  
Mylari, Banavara L., Waterford, CT, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003050301	A1	20030313
APPLICATION INFO.:	US 2002-280388	A1	20021025 (10)
RELATED APPLN. INFO.:	Division of Ser. No. US 2000-727958, filed on 1 Dec 2000, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-169380P	19991207 (60) <--
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	PFIZER INC., PATENT DEPARTMENT, MS8260-1611, EASTERN POINT ROAD, GROTON, CT, 06340	
NUMBER OF CLAIMS:	43	
EXEMPLARY CLAIM:	1	
LINE COUNT:	1068	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention is directed to methods, pharmaceutical compositions and kits comprising an aldose reductase inhibitor (ARI), a prodrug thereof or a pharmaceutically acceptable salt of said ARI or said prodrug and an antihypertensive agent, a prodrug thereof or a pharmaceutically acceptable salt of said antihypertensive agent or said prodrug. This invention further relates to methods of using those pharmaceutical compositions for the treatment of diabetic complications such as diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, myocardial infarction, cataracts and diabetic cardiomyopathy.

PRAI US 1999-169380P 19991207 (60) <--

IT Ion **channel** blockers  
(**calcium**; compns. containing aldose reductase inhibitors and antihypertensive agents for treatment of diabetic complications)

IT **Heart**, disease  
(diabetic **cardiomyopathy**; compns. containing aldose reductase inhibitors and antihypertensive agents for treatment of diabetic complications)

IT **Heart**, disease  
(infarction; compns. containing aldose reductase inhibitors and antihypertensive agents for treatment of diabetic complications)

IT 52-53-9, Verapamil 73-48-3, Bendroflumethiazide 2609-46-3, Amiloride 19216-56-9, Prazosin 21829-25-4, Nifedipine 35795-16-5, Trimazosin 39562-70-4, Nitrendipine 42399-41-7, Diltiazem 55985-32-5, Nicardipine 63675-72-9, Nisoldipine 66085-59-4, Nimodipine 72509-76-3, Felodipine 72956-09-3, Carvedilol 74191-85-8, Doxazosin 75695-93-1, Isradipine 82159-09-9, Epalrestat 88150-42-9, Amlodipine 103890-78-4, Lacidipine 110703-94-1, Zopolrestat 112733-06-9, Zenarestat **116644-53-2**, Mibefradil 123122-54-3, Candoxatrilat 123122-55-4, Candoxatril 129688-50-2, Minalrestat 129981-36-8, Sampatrilat 136087-85-9, Fidarestat 143162-65-6, SPR-210 167305-00-2, Omapatrilat  
(compns. containing aldose reductase inhibitors and antihypertensive agents for treatment of diabetic complications)

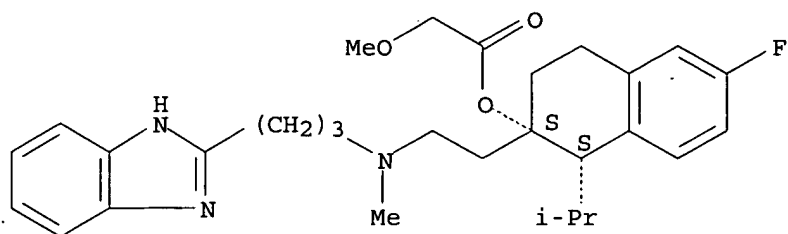
IT **116644-53-2**, Mibefradil  
(compns. containing aldose reductase inhibitors and antihypertensive agents for treatment of diabetic complications)

RN 116644-53-2 USPATFULL

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-

methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 70 OF 198    USPATFULL on STN  
 ACCESSION NUMBER:    2003:60288    USPATFULL  
 TITLE:    Calcium channel compositions and methods  
 INVENTOR(S):    Williams, Mark E., Carlsbad, CA, United States  
                   Stauderman, Kenneth A., San Diego, CA, United States  
                   Harpold, Michael M., El Cajon, CA, United States  
 PATENT ASSIGNEE(S):    Merck & Co., Inc., Rahway, NJ, United States (U.S.  
                                   corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6528630	B1	20030304	
APPLICATION INFO.:	US 1997-984709		19971203	(8) <--
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	GRANTED			
PRIMARY EXAMINER:	Carlson, Karen Cochrane			
ASSISTANT EXAMINER:	Robinson, Patricia			
LEGAL REPRESENTATIVE:	Coppola, Joseph A., Tribble, Jack L.			
NUMBER OF CLAIMS:	50			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	0 Drawing Figure(s); 0 Drawing Page(s)			
LINE COUNT:	4305			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Isolated nucleic acid encoding calcium channel  $\alpha$ .sub.1F-subunits, including subunits encoded by nucleic acid that arises as splice variants of primary transcripts, is provided. Cells and vectors containing the nucleic acid and methods for identifying compounds that modulate the activity of calcium channels that contain  $\alpha$ .sub.1F-subunits are also provided.

AI US 1997-984709    19971203 (8) <--

ST low voltage calcium channel cDNA cloning expression;  
 T type calcium channel cDNA cloning expression; drug  
 screening T type calcium channel

IT Animal cell line  
 (African green monkey, expression host for calcium  
 channel cDNAs; low-voltage activated calcium  
 channel proteins and cDNAs encoding them and development of  
 calcium channel blockers)

IT Animal cell line  
 (CHO, expression host for calcium channel cDNAs;  
 low-voltage activated calcium channel proteins and  
 cDNAs encoding them and development of calcium  
 channel blockers)

IT Animal cell line  
 (Hek 293, expression host for calcium channel

IT Animal cell line  
(L, expression host for **calcium channel** cDNAs;  
low-voltage activated **calcium channel** proteins and  
cDNAs encoding them and development of **calcium**  
**channel** blockers)

IT **Calcium channel**  
(T-type; low-voltage activated **calcium channel**  
proteins and cDNAs encoding them and development of **calcium**  
**channel** blockers)

IT Gene, animal  
(cDNA; low-voltage activated **calcium channel**  
proteins and cDNAs encoding them and development of **calcium**  
**channel** blockers)

IT Blood vessel, disease

IT Liver, disease  
(**calcium channel** blockers for treatment of;  
low-voltage activated **calcium channel** proteins and  
cDNAs encoding them and development of **calcium**  
**channel** blockers)

IT Ion **channel** blockers  
(**calcium**; low-voltage activated **calcium**  
**channel** proteins and cDNAs encoding them and development of  
**calcium channel** blockers)

IT **Cardiovascular system**

IT **Endocrine system**

IT **Nervous system**

IT **Respiratory tract**

IT **Urinary tract**  
(disease, **calcium channel** blockers for treatment  
of; low-voltage activated **calcium channel** proteins  
and cDNAs encoding them and development of **calcium**  
**channel** blockers)

IT cDNA sequences  
(for T-type **calcium channels** of human; low-voltage  
activated **calcium channel** proteins and cDNAs  
encoding them and development of **calcium channel**  
blockers)

IT Probes (nucleic acid)  
(for detection of **calcium channel** genes;  
low-voltage activated **calcium channel** proteins and  
cDNAs encoding them and development of **calcium**  
**channel** blockers)

IT Drug screening  
(low-voltage activated **calcium channel** proteins and  
cDNAs encoding them and development of **calcium**  
**channel** blockers)

IT Protein sequences  
(of T-type **calcium channels** of human; low-voltage  
activated **calcium channel** proteins and cDNAs  
encoding them and development of **calcium channel**  
blockers)

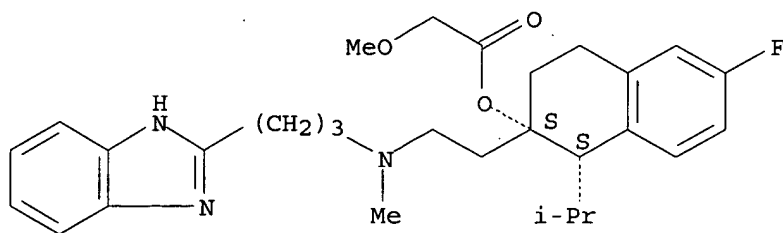
IT Egg  
(oocyte, *Xenopus laevis*, expression host for **calcium**  
**channel** cDNAs; low-voltage activated **calcium**  
**channel** proteins and cDNAs encoding them and development of  
**calcium channel** blockers)

IT Plasmid vectors



- (pHBCaH $\alpha$ 2A, cDNA for **calcium channel  $\alpha$ 2** subunit on; low-voltage activated **calcium channel** proteins and cDNAs encoding them and development of **calcium channel blockers**)
- IT Plasmid vectors  
(pHBCaH $\beta$ 1aRBS(A), cDNA for **calcium channel  $\beta$ 1** subunit on; low-voltage activated **calcium channel** proteins and cDNAs encoding them and development of **calcium channel blockers**)
- IT Plasmid vectors  
(pVDCCIII(A), cDNA for **calcium channel  $\alpha$ 1D** subunit on; low-voltage activated **calcium channel** proteins and cDNAs encoding them and development of **calcium channel blockers**)
- IT 221650-96-0 226981-32-4 226981-37-9  
(amino acid sequence; low-voltage activated **calcium channel** proteins and cDNAs encoding them and development of **calcium channel blockers**)
- IT 2609-46-3 7440-02-0, Nickel, biological studies 7440-43-9, Cadmium, biological studies 116644-53-2, Mibefradil  
(as **calcium channel** antagonist; low-voltage activated **calcium channel** proteins and cDNAs encoding them and development of **calcium channel blockers**)
- IT 226981-31-3 226981-33-5 226981-34-6 226981-35-7 226981-36-8  
(nucleotide sequence; low-voltage activated **calcium channel** proteins and cDNAs encoding them and development of **calcium channel blockers**)
- IT 116644-53-2, Mibefradil  
(as **calcium channel** antagonist; low-voltage activated **calcium channel** proteins and cDNAs encoding them and development of **calcium channel blockers**)
- RN 116644-53-2 USPATFULL
- CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 71 OF 198 USPATFULL on STN  
 ACCESSION NUMBER: 2002:266318 USPATFULL  
 TITLE: Methods and compositions for enhancing pharmaceutical treatments  
 INVENTOR(S): Newman, Michael J., San Diego, CA, UNITED STATES  
 Dixon, William Ross, La Jolla, CA, UNITED STATES

NUMBER KIND DATE

PATENT INFORMATION: US 2002147197 A1 20021010  
 APPLICATION INFO.: US 2002-104549 A1 20020320 (10)  
 RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-684293, filed  
 on 6 Oct 2000, PENDING

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1999-158322P	19991008 (60)	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	ONTOGEN CORPORATION, PATENT DEPARTMENT, 6451 EL CAMINO REAL, CARLSBAD, CA, 92009		
NUMBER OF CLAIMS:	231		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	8 Drawing Page(s)		
LINE COUNT:	3737		
CAS INDEXING IS AVAILABLE FOR THIS PATENT.			

AB Improved methods are provided for therapeutic and/or preventative treatment to a mammal in which the mammal is protected against the toxicity of active pharmaceutical agents that (i) bind to or are substrates for P-gp, (ii) are taxane analogues, and/or (iii) are inhibitors of tubulin disassembly. Additionally provided are compositions and methods useful for treating cell proliferative disorders. Further provided are methods of increasing the bioavailability of therapeutic and/or preventative treatments in a mammal. Particular embodiments are directed to increasing such bioavailability across the blood-brain barrier.

PRAI US 1999-158322P 19991008 (60) <--

IT Ion **channel** blockers  
 (calcium; methods and compns. for enhancing pharmaceutical treatments)

IT 90729-43-4, Ebastine 90729-43-4D, Ebastine, derivs., analogs, and metabolites 93957-54-1, Fluvastatin 93957-54-1D, Fluvastatin, derivs., analogs, and metabolites 97682-44-5, Irinotecan 97682-44-5D, Irinotecan, derivs., analogs, and metabolites 99614-02-5, Ondansetron 99614-02-5D, Ondansetron, derivs., analogs, and metabolites 100986-85-4, Levofloxacin 100986-85-4D, Levofloxacin, derivs., analogs, and metabolites 104987-11-3, Tacrolimus 104987-11-3D, Tacrolimus, derivs., analogs, and metabolites 105650-23-5, 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine 105650-23-5D, 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, derivs., analogs, and metabolites 106941-25-7, Adefovir 106941-25-7D, Adefovir, derivs., analogs, and metabolites 109581-73-9 109581-73-9D, derivs., analogs, and metabolites 110871-86-8, Sparfloxacin 110871-86-8D, Sparfloxacin, derivs., analogs, and metabolites 111865-30-6 111865-30-6D, derivs., analogs, and metabolites 113507-06-5, Moxidectin 113507-06-5D, Moxidectin, derivs., analogs, and metabolites 114798-26-4, Losartan 114798-26-4D, Losartan, derivs., analogs, and metabolites 114977-28-5, Docetaxel 114977-28-5D, Docetaxel, derivs., analogs, and metabolites 115268-43-4, Laulimalide 115268-43-4D, Laulimalide, derivs., analogs, and metabolites **116644-53-2**, Mibefradil **116644-53-2D**, Mibefradil, derivs., analogs, and metabolites 119914-60-2, Grepafloxacin 119914-60-2D, Grepafloxacin, derivs., analogs, and metabolites 121584-18-7, PSC833 121584-18-7D, PSC833, derivs., analogs, and metabolites 123040-69-7, Azasetron 123040-69-7D, Azasetron, derivs., analogs, and metabolites 123948-87-8, Topotecan 123948-87-8D, Topotecan, derivs., analogs, and metabolites 127779-20-8D, Saquinavir, derivs., analogs, and metabolites 127785-64-2, Aureobasidin A 127785-64-2D, Aureobasidin A, derivs., analogs, and metabolites 127943-53-7, Discodermolide 127943-53-7D,

Discodermolide, derivs., analogs, and metabolites 134446-66-5, BW 1288U89 134446-66-5D, BW 1288U89, derivs., analogs, and metabolites 134523-00-5, Atorvastatin 134523-00-5D, Atorvastatin, derivs., analogs, and metabolites 143322-58-1, Eletriptan 143322-58-1D, Eletriptan, derivs., analogs, and metabolites 145599-86-6, Cerivastatin 145599-86-6D, Cerivastatin, derivs., analogs, and metabolites 146426-40-6, Flavopiridol 146426-40-6D, Flavopiridol, derivs., analogs, and metabolites 148504-34-1, Calcein-AM 148504-34-1D, Calcein-AM, derivs., analogs, and metabolites 150378-17-9, Indinavir 150378-17-9D, Indinavir, derivs., analogs, and metabolites 152459-95-5, Imatinib 152459-95-5D, Imatinib, derivs., analogs, and metabolites 155213-67-5, Ritonavir 155213-67-5D, Ritonavir, derivs., analogs, and metabolites 159989-64-7, Nelfinavir 159989-64-7D, Nelfinavir, derivs., analogs, and metabolites 161814-49-9, Amprenavir 161814-49-9D, Amprenavir, derivs., analogs, and metabolites 174545-76-7, Eleutherobin 174545-76-7D, Eleutherobin, derivs., analogs, and metabolites 178309-91-6, UK 224671 178309-91-6D, UK 224671, derivs., analogs, and metabolites 186348-23-2, BAY59-8862 186348-23-2D, BAY59-8862, derivs., analogs, and metabolites 198711-61-4, BW 1019W91 198711-61-4D, BW 1019W91, derivs., analogs, and metabolites 198711-62-5, BW 1379W91 198711-62-5D, BW 1379W91, derivs., analogs, and metabolites 198711-63-6, BW 1351W91 198711-63-6D, BW 1351W91, derivs., analogs, and metabolites 216227-21-3 216227-22-4 216227-23-5 216227-24-6 216227-25-7 216227-26-8 216227-27-9 216227-28-0 216227-29-1 216227-30-4 216227-54-2 216227-54-2D, derivs., analogs, and metabolites 220578-59-6, Gemtuzumab ozogamicin 220578-59-6D, Gemtuzumab ozogamicin, derivs., analogs, and metabolites 270076-60-3, Pristinamycin 270076-60-3D, Pristinamycin, derivs., analogs, and metabolites 334865-65-5 467419-00-7D, derivs., analogs, and metabolites

(methods and compns. for enhancing pharmaceutical treatments)

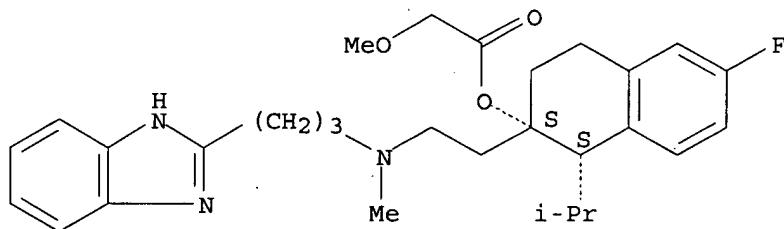
IT 116644-53-2, Mibefradil 116644-53-2D, Mibefradil, derivs., analogs, and metabolites

(methods and compns. for enhancing pharmaceutical treatments)

RN 116644-53-2 USPATFULL

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

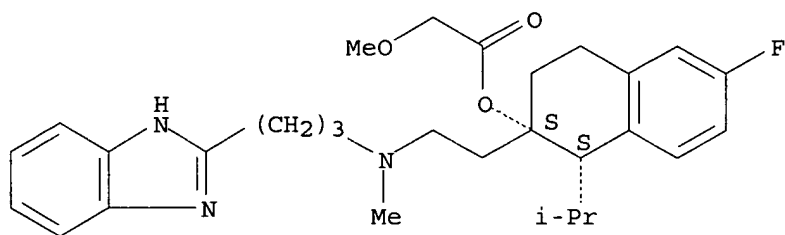
Absolute stereochemistry.



RN 116644-53-2 USPATFULL

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 72 OF 198    USPATFULL on STN  
 ACCESSION NUMBER:    2002:186125    USPATFULL  
 TITLE:    Combination therapy  
 INVENTOR(S):    Scott, Robert Andrew Donald, Riverside, CT, UNITED STATES  
 PATENT ASSIGNEE(S):    Pfizer Inc. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002099046	A1	20020725
APPLICATION INFO.:	US 2001-45329	A1	20011023 (10) <--
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2000-513887, filed on 25 Feb 2000, ABANDONED		

	NUMBER	DATE
PRIORITY INFORMATION:	WO 1998-IB1230	19980811 <--
	US 1997-57276P	19970829 (60) <--
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Gregg C. Benson, Pfizer Inc., Patent Department, Box 519, Eastern Point Road, Groton, CT, 06340	
NUMBER OF CLAIMS:	67	
EXEMPLARY CLAIM:	1	
LINE COUNT:	1775	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB    This invention relates to pharmaceutical combinations of atorvastatin or a pharmaceutically acceptable salt thereof and antihypertensive agents, kits containing such combinations and methods of using such combinations to treat subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and to treat subjects presenting with symptoms of cardiac risk, including humans. This invention also relates to additive and synergistic combinations of atorvastatin or a pharmaceutically acceptable salt thereof and antihypertensive agents whereby those synergistic combinations are useful in treating subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and those subjects presenting with symptoms of cardiac risk, including humans.

AI    US 2001-45329    A1    20011023 (10)    <--

PRAI    WO 1998-IB1230    19980811    <--

PRAI    US 1997-57276P    19970829 (60)    <--

IT    Ion **channel** blockers

(**calcium**; combination therapy comprising atorvastatin and antihypertensive agent)

IT    **Heart**, disease

(failure; combination therapy comprising atorvastatin and antihypertensive agent for **cardiac** risk management)

IT    52-53-9, Verapamil    73-48-3, Bendroflumethiazide    2609-46-3, Amiloride

19216-56-9, Prazosin 21829-25-4, Nifedipine 35795-16-5, Trimazosin  
 39562-70-4, Nitrendipine 42399-41-7, Diltiazem 55985-32-5,  
 Nicardipine 62571-86-2, Captopril 63675-72-9, Nisoldipine  
 66085-59-4, Nimodipine 72509-76-3, Felodipine 72956-09-3, Carvedilol  
 74191-85-8, Doxazosin 75695-93-1, Isradipine 75847-73-3, Enalapril  
 76547-98-3, Lisinopril 82834-16-0, Perindopril 85441-61-8, Quinapril  
 86541-75-5, Benazepril 87679-37-6, Trandolapril 98048-97-6,  
 Fosinopril 103890-78-4, Lacidipine 114798-26-4, Losartan  
 116644-53-2, Mibefradil 134523-00-5, Atorvastatin  
 134523-03-8, Atorvastatin calcium 137862-53-4, Valsartan 138402-11-6,  
 Irbesartan

(combination therapy comprising atorvastatin and antihypertensive agent)

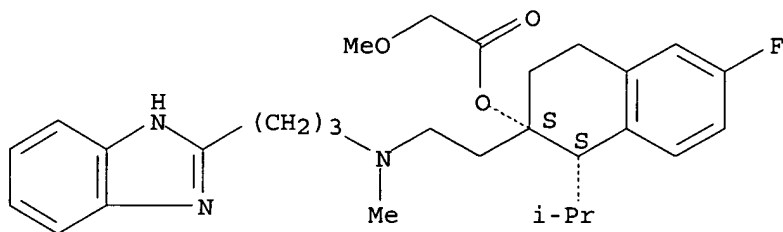
IT 116644-53-2, Mibefradil

(combination therapy comprising atorvastatin and antihypertensive agent)

RN 116644-53-2 USPATFULL

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 73 OF 198 USPATFULL on STN

ACCESSION NUMBER: 2002:133882 USPATFULL

TITLE: Combination of aldose reductase inhibitors and antihypertensive agents for the treatment of diabetic complications

INVENTOR(S): Mylari, Banavara L., Waterford, CT, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002068740	A1	20020606
APPLICATION INFO.:	US 2000-727958	A1	20001201 (9) <--

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-169380P	19991207 (60) <--
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Gregg C. Benson, Pfizer Inc., MS 4159, Patent Department, Groton, CT, 06340	
NUMBER OF CLAIMS:	43	
EXEMPLARY CLAIM:	1	
LINE COUNT:	1063	

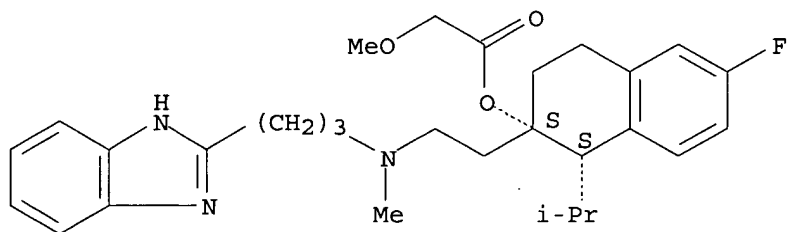
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention is directed to methods, pharmaceutical compositions and kits comprising an aldose reductase inhibitor (ARI), a prodrug thereof or a pharmaceutically acceptable salt of said ARI or said prodrug and an

antihypertensive agent, a prodrug thereof or a pharmaceutically acceptable salt of said antihypertensive agent or said prodrug. This invention further relates to methods of using those pharmaceutical compositions for the treatment of diabetic complications such as diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, myocardial infarction, cataracts and diabetic cardiomyopathy.

AI US 2000-727958 A1 20001201 (9) <--  
 PRAI US 1999-169380P 19991207 (60) <--  
 IT Ion **channel** blockers  
     (**calcium**; compns. containing aldose reductase inhibitors and antihypertensive agents for treatment of diabetic complications)  
 IT **Heart**, disease  
     (diabetic **cardiomyopathy**; compns. containing aldose reductase inhibitors and antihypertensive agents for treatment of diabetic complications)  
 IT **Heart**, disease  
     (infarction; compns. containing aldose reductase inhibitors and antihypertensive agents for treatment of diabetic complications)  
 IT 52-53-9, Verapamil 73-48-3, Bendroflumethiazide 2609-46-3, Amiloride 19216-56-9, Prazosin 21829-25-4, Nifedipine 35795-16-5, Trimazosin 39562-70-4, Nitrendipine 42399-41-7, Diltiazem 55985-32-5, Nicardipine 63675-72-9, Nisoldipine 66085-59-4, Nimodipine 72509-76-3, Felodipine 72956-09-3, Carvedilol 74191-85-8, Doxazosin 75695-93-1, Isradipine 82159-09-9, Epalrestat 88150-42-9, Amlodipine 103890-78-4, Lacidipine 110703-94-1, Zopolrestat 112733-06-9, Zenarestat **116644-53-2**, Mibefradil 123122-54-3, Candoxatrilat 123122-55-4, Candoxatril 129688-50-2, Minalrestat 129981-36-8, Sampatrilat 136087-85-9, Fidarestat 143162-65-6, SPR-210 167305-00-2, Omapatrilat  
     (compns. containing aldose reductase inhibitors and antihypertensive agents for treatment of diabetic complications)  
 IT **116644-53-2**, Mibefradil  
     (compns. containing aldose reductase inhibitors and antihypertensive agents for treatment of diabetic complications)  
 RN 116644-53-2 USPATFULL  
 CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 74 OF 198 USPATFULL on STN  
 ACCESSION NUMBER: 2002:43207 USPATFULL  
 TITLE: Multi-well plate and electrode assemblies for ion channel assays  
 INVENTOR(S): Maher, Michael P., San Diego, CA, UNITED STATES  
                   Gonzalez, Jesus E., III, San Diego, CA, UNITED STATES

NUMBER KIND DATE

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PATENT INFORMATION:  US 2002025573      A1    20020228
APPLICATION INFO.:   US 2001-804458      A1    20010312  (9)    <--

                        NUMBER      DATE
                        -----
PRIORITY INFORMATION: US 2000-217671P    20000710 (60)    <--
DOCUMENT TYPE:        Utility
FILE SEGMENT:         APPLICATION
LEGAL REPRESENTATIVE: KNOBBE MARTENS OLSON & BEAR LLP, 620 NEWPORT CENTER
                      DRIVE, SIXTEENTH FLOOR, NEWPORT BEACH, CA, 92660
NUMBER OF CLAIMS:     22
EXEMPLARY CLAIM:      1
NUMBER OF DRAWINGS:    35 Drawing Page(s)
LINE COUNT:           4720
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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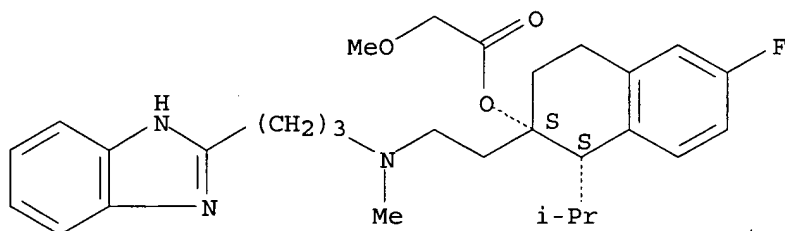
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AB    Plate and electrode assemblies include configurations allowing for
      relatively uniform electric field production. The electrodes may
      comprise strips of conductive material plated onto the bottom surface of
      sample wells or they may comprise plate electrodes extending down into
      the well. In some embodiments, the electric field strength varies by
      less than about 10% from a mean field intensity over at least about 20%
      of the surface area of the bottom surface of a sample well.
AI    US 2001-804458      A1    20010312 (9)    <--
PRAI  US 2000-217671P    20000710 (60)    <--
ST    ion channel assay elec field transmembrane potential; calcium
      channel elec stimulation FRET probe
IT    Calcium channel
      (L-type; ion channel assay methods using repetitive application of
      elec. fields to set transmembrane potential)
IT    Ion channel blockers
      (calcium, L-type; ion channel assay methods using repetitive
      application of elec. fields to set transmembrane potential)
IT    Muscle
      (cardiac, cells of; ion channel assay methods using
      repetitive application of elec. fields to set transmembrane potential)
IT    Calcium channel
IT    Chloride channel
IT    Potassium channel
      (ion channel assay methods using repetitive application of
      elec. fields to set transmembrane potential)
IT    Calcium channel
IT    Sodium channel
      (voltage-gated; ion channel assay methods using repetitive application
      of elec. fields to set transmembrane potential)
IT    50-48-6, Amitriptyline  52-53-9, Verapamil  57-41-0, Phenytoin
      66-40-0, Tetraethylammonium  85-79-0, Dibucaine  91-64-5, Coumarin
      94-24-6, Tetracaine  137-58-6, Lidocaine  146-48-5, Yohimbine
      404-86-4, Capsaicin  2609-46-3, Amiloride  4368-28-9, Tetrodotoxin
      10361-37-2, Barium chloride, biological studies  21829-25-4
      31828-71-4, Mexiletine  35523-89-8, Saxitoxin  38396-39-3, Bupivacaine
      47623-98-3, DiSBAC2(3)  66085-59-4, Nimodipine  68844-77-9, Astemizole
      84057-84-1, Lamotrigine 116644-53-2, Mibefradil  169970-60-9
      393782-57-5, CC2-DMPE
      (ion channel assay methods using repetitive application of elec. fields
      to set transmembrane potential)
IT    116644-53-2, Mibefradil
      (ion channel assay methods using repetitive application of elec. fields
      to set transmembrane potential)
RN    116644-53-2  USPATFULL

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CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 75 OF 198 USPATFULL on STN  
 ACCESSION NUMBER: 2001:224230 USPATFULL  
 TITLE: Mibefradil analogues and their use  
 INVENTOR(S): Li, Ming, Mobile, AL, United States  
 Hansen, John Bondo, Jyderup, Denmark  
 Tagmose, Tina Moller, Ballerup, Denmark

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2001049447	A1	20011206	<--
APPLICATION INFO.:	US 2001-818398	A1	20010327 (9)	<--
RELATED APPLN. INFO.:	Continuation of Ser. No. WO 2001-DK128, filed on 23 Feb 2001, UNKNOWN			

	NUMBER	DATE	
PRIORITY INFORMATION:	DK 2000-293	20000225	<--
	US 2000-185583P	20000228 (60)	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Steve T. Zelson, Esq., Novo Nordisk of North America, Inc., Suite 6400, 405 Lexington Avenue, New York, NY, 10174-6401		
NUMBER OF CLAIMS:	22		
EXEMPLARY CLAIM:	1		
LINE COUNT:	682		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to mibefradil analogues, to compositions comprising the compounds and their use in therapy, e.g. in the treatment and/or prevention of type 1 and type 2 diabetes as well as microvascular or macrovascular diseases associated with diabetes.

PI US 2001049447 A1 20011206 <--

AI US 2001-818398 A1 20010327 (9) <--

PRAI DK 2000-293 20000225 <--

PRAI US 2000-185583P 20000228 (60) <--

IT **Heart**, disease

(infarction, macrovascular diseases associated with; preparation of mibefradil

analogs for use in therapy of type 1 and type 2 diabetes)

IT 79-30-1, Isobutyryl chloride 638-29-9, Valeroyl chloride

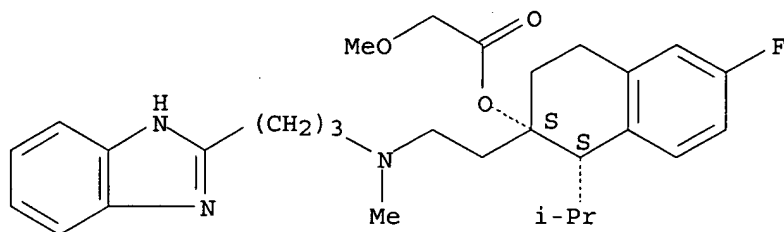
**116666-63-8**, Mibefradil dihydrochloride

(preparation of mibefradil analogs for use in therapy of type 1 and type 2 diabetes)



IT 116666-63-8, Mibefradil dihydrochloride  
 (preparation of mibefradil analogs for use in therapy of type 1 and type 2 diabetes)  
 RN 116666-63-8 USPATFULL  
 CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 HCl

L103 ANSWER 76 OF 198 USPATFULL on STN  
 ACCESSION NUMBER: 2001:147970 USPATFULL  
 TITLE: Methods for remodeling neuronal and cardiovascular pathways  
 INVENTOR(S): Adams, Michael A., Kingston, Canada  
 Heaton, Jeremy P. W., Gananoque, Canada  
 PATENT ASSIGNEE(S): Queen's University at Kingston, Kingston, Canada  
 (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6284763	B1	20010904	<--
APPLICATION INFO.:	US 1999-382749		19990825 (9)	<--

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1998-98178P	19980826 (60)	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	GRANTED		
PRIMARY EXAMINER:	Reamer, James H.		
LEGAL REPRESENTATIVE:	Steeg, Carol Miernicki, Scribner, Stephen J., Janssen, Jerry F.		
NUMBER OF CLAIMS:	33		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	8 Drawing Figure(s); 6 Drawing Page(s)		
LINE COUNT:	1099		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

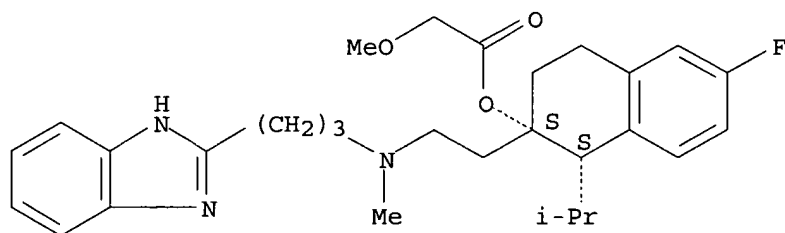
AB The present invention provides a method of administration of an agent which acts to remodel neuronal or vascular pathways for the long term management of sexual dysfunction in both males and females. In a preferred embodiment, the invention provides a method of ameliorating or reversing pathogenic vascular degradative modeling in the ilio-hypogastric-pudendal arterial bed and genitalia comprising

administering to a human patient in need of such treatment a therapeutically effective amount of an anti-pressor agent. The anti-pressor agent comprises one or more compounds selected from the therapeutic classes of direct vasodilators such as hydralazine and NO donors, ACE inhibitors, angiotensin-II receptor antagonists,  $\alpha$ .sub.1 -adrenergic receptor antagonists,  $\beta$ -adrenergic receptor antagonists, calcium channel blockers, and phosphodiesterase inhibitors. The anti-pressor agent may be co-administered with a diuretic compound, and is administered either chronically at low dose, or for short periods of time at doses higher than are typically used for the treatment of hypertension. In certain embodiments of the method of the invention, the anti-pressor agent is co-administered with a diuretic agent and/or prostaglandin-E.sub.1.

PI	US 6284763	B1	20010904	<--
AI	US 1999-382749		19990825 (9)	<--
PRAI	US 1998-98178P		19980826 (60)	<--
ST	antipressor <b>cardiovascular</b> neuronal remodeling sexual dysfunction; diuretic antipressor <b>cardiovascular</b> neuronal remodeling sexual dysfunction; prostaglandin antipressor <b>cardiovascular</b> neuronal remodeling sexual dysfunction			
IT	Angiotensin receptors (AT1, antagonists; anti-pressor agents and methods for remodeling neuronal and <b>cardiovascular</b> pathways for long term management of sexual dysfunction)			
IT	Antihypertensives			
IT	<b>Cardiovascular</b> agents			
IT	Diuretics			
IT	Nervous system agents			
IT	Reproductive tract			
IT	Vasodilators (anti-pressor agents and methods for remodeling neuronal and <b>cardiovascular</b> pathways for long term management of sexual dysfunction)			
IT	Ion <b>channel</b> blockers ( <b>calcium</b> ; anti-pressor agents and methods for remodeling neuronal and <b>cardiovascular</b> pathways for long term management of sexual dysfunction)			
IT	Sexual behavior (disorder; anti-pressor agents and methods for remodeling neuronal and <b>cardiovascular</b> pathways for long term management of sexual dysfunction)			
IT	Artery (ilio-hypogastric-pudendal arterial bed; anti-pressor agents and methods for remodeling neuronal and <b>cardiovascular</b> pathways for long term management of sexual dysfunction)			
IT	Blood vessel (pathogenic vascular degradative modeling; anti-pressor agents and methods for remodeling neuronal and <b>cardiovascular</b> pathways for long term management of sexual dysfunction)			
IT	Penis (penile vascular bed; anti-pressor agents and methods for remodeling neuronal and <b>cardiovascular</b> pathways for long term management of sexual dysfunction)			
IT	Adrenoceptor antagonists ( $\alpha$ 1-; anti-pressor agents and methods for remodeling neuronal and <b>cardiovascular</b> pathways for long term management of sexual dysfunction)			
IT	Adrenoceptor antagonists ( $\beta$ -; anti-pressor agents and methods for remodeling neuronal and <b>cardiovascular</b> pathways for long term management of sexual dysfunction)			

- dysfunction)
- IT 9012-42-4, Adenyl cyclase 9054-75-5, Guanylyl cyclase  
(activators; anti-pressor agents and methods for remodeling neuronal  
and **cardiovascular** pathways for long term management of  
sexual dysfunction)
- IT 10102-43-9, Nitric oxide, biological studies  
(and NO donors; anti-pressor agents and methods for remodeling neuronal  
and **cardiovascular** pathways for long term management of  
sexual dysfunction)
- IT 390-28-3, Methoxamine 11000-17-2, Vasopressin 11128-99-7, Angiotensin  
II  
(anti-pressor agents and methods for remodeling neuronal and  
**cardiovascular** pathways for long term management of sexual  
dysfunction)
- IT 50-60-2, Phentolamine 52-53-9, Verapamil 55-63-0, Glyceryl trinitrate  
59-96-1, Phenoxymethamine 78-11-5, Pentaerythritol tetranitrate  
86-54-4, Hydralazine 87-33-2, Isosorbide dinitrate 745-65-3,  
Prostaglandin E1 835-31-4, Naphazoline 4205-90-7, Clonidine  
14402-89-2, Sodium nitroprusside 16051-77-7, Isosorbide 5-mononitrate  
19216-56-9, Prazosin 21829-25-4, Nifedipine 25717-80-0, Molsidomine  
26844-12-2, Indoramin 33876-97-0, 3-Morpholinomethylamine 34661-75-1,  
Urapidil 35795-16-5, Trimazosin 36894-69-6 42399-41-7, Diltiazem  
42794-76-3, Midodrine 53054-07-2 55985-32-5, Nicardipine  
57564-91-7, S-Nitrosoglutathione 60719-84-8, Amrinone 62571-86-2,  
Captopril 63590-64-7, Terazosin 64706-54-3, Bepridil 66085-59-4,  
Nimodipine 66575-29-9, Forskolin 66711-21-5, Apraclonidine  
72822-12-9, Dapiprazole 72956-09-3, Carvedilol 74191-85-8, Doxazosin  
74258-86-9, Alacepril 75847-73-3, Enalapril 76547-98-3, Lisinopril  
79032-48-7, S-Nitroso-N-acetylpenicillamine 80755-51-7, Bunazosin  
81403-80-7, Alfuzosin 82834-16-0, Perindopril 82924-03-6, Pentopril  
83435-66-9, Delapril 83647-97-6, Spirapril 85441-61-8, Quinapril  
85856-54-8, Moveltipril 86541-75-5, Benazepril 87333-19-5, Ramipril  
87679-37-6, Trandolapril 88768-40-5, Cilazapril 89371-37-9, Imidapril  
98048-97-6, Fosinopril 103775-10-6, Moexipril 103890-78-4, Lacidipine  
106133-20-4, Tamsulosin 109214-55-3, Libenzapril 111223-26-8,  
Ceronapril 111902-57-9, Temocapril 114798-26-4, Losartan  
**116644-53-2**, Mibefradil 133040-01-4, Eprosartan 137862-53-4,  
Valsartan 138402-11-6, Irbesartan 139755-83-2, Sildenafil  
170632-47-0, YC-1  
(anti-pressor agents and methods for remodeling neuronal and  
**cardiovascular** pathways for long term management of sexual  
dysfunction)
- IT 9015-82-1 9025-82-5, Phosphodiesterase  
(inhibitors; anti-pressor agents and methods for remodeling neuronal  
and **cardiovascular** pathways for long term management of  
sexual dysfunction)
- IT **116644-53-2**, Mibefradil  
(anti-pressor agents and methods for remodeling neuronal and  
**cardiovascular** pathways for long term management of sexual  
dysfunction)
- RN 116644-53-2 USPATFULL
- CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-  
yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-  
methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 77 OF 198    USPATFULL on STN  
 ACCESSION NUMBER:    2001:121484    USPATFULL  
 TITLE:    Method for treating androgen-related conditions  
 INVENTOR(S):    Waldstreicher, Joanne, Scotch Plains, NJ, United States  
                   Wang, Daniel Z., Edison, NJ, United States  
 PATENT ASSIGNEE(S):    Merck & Co., Inc., Rahway, NJ, United States (U.S.  
                                  corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6268377	B1	20010731	<--
APPLICATION INFO.:	US 1999-401135		19990922 (9)	<--

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1998-102018P	19980928 (60)	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	GRANTED		
PRIMARY EXAMINER:	Fay, Zohreh		
ASSISTANT EXAMINER:	Kwon, Brian-Yong		
LEGAL REPRESENTATIVE:	Fitch, Catherine D., Durette, Philippe L., Winokur, Melvin		
NUMBER OF CLAIMS:	19		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	4 Drawing Figure(s); 2 Drawing Page(s)		
LINE COUNT:	1028		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB    The present invention provides for the combined use of 5 $\alpha$ -reductase inhibitors together with calcium channel blockers for the treatment of benign prostatic hyperplasia (BPH), prostate cancer, prostatitis, hematuria, and other androgen related disorders, including prostatitis and the prevention of prostate cancer. This invention provides a method of treatment which is useful in the treatment of benign prostatic hyperplasia, prostatitis, and/or the prevention and treatment of prostatic cancer, as well as in the treatment of prostatitis and hematuria. This invention also provides a pharmaceutical composition which is useful in the treatment of benign prostatic hyperplasia, prostatitis, hematuria and/or the prevention and treatment of prostatic cancer, wherein the pharmaceutical composition comprises the combination of a 5 $\alpha$ -reductase inhibitor and a calcium channel blocking agent.

PI	US 6268377	B1	20010731	<--
AI	US 1999-401135		19990922 (9)	<--
PRAI	US 1998-102018P		19980928 (60)	<--
ST	androgen condition steroid reductase inhibitor combination; <b>calcium channel</b> blocker combination androgen disorder; benign prostatic hyperplasia steroid reductase inhibitor <b>calcium channel</b> blocker; prostate cancer steroid reductase inhibitor			

- calcium channel blocker; prostatitis steroid reductase inhibitor calcium channel blocker; hematuria steroid reductase inhibitor calcium channel blocker
- IT Urine  
(acute urinary retention; combined use of 5 $\alpha$ -reductase inhibitors and calcium channel blockers for treating androgen-related conditions)
- IT Prostate gland  
(benign hyperplasia; combined use of 5 $\alpha$ -reductase inhibitors and calcium channel blockers for treating androgen-related conditions)
- IT Ion channel blockers  
(calcium; combined use of 5 $\alpha$ -reductase inhibitors and calcium channel blockers for treating androgen-related conditions)
- IT Drug delivery systems  
(combined use of 5 $\alpha$ -reductase inhibitors and calcium channel blockers for treating androgen-related conditions)
- IT Androgens
- IT Prostate-specific antigen  
(combined use of 5 $\alpha$ -reductase inhibitors and calcium channel blockers for treating androgen-related conditions)
- IT Urine  
(hematuria; combined use of 5 $\alpha$ -reductase inhibitors and calcium channel blockers for treating androgen-related conditions)
- IT Prostate gland
- IT Prostate gland  
(neoplasm, inhibitors; combined use of 5 $\alpha$ -reductase inhibitors and calcium channel blockers for treating androgen-related conditions)
- IT Drug delivery systems  
(oral; combined use of 5 $\alpha$ -reductase inhibitors and calcium channel blockers for treating androgen-related conditions)
- IT Antitumor agents  
(prostate gland; combined use of 5 $\alpha$ -reductase inhibitors and calcium channel blockers for treating androgen-related conditions)
- IT Prostate gland  
(prostatitis; combined use of 5 $\alpha$ -reductase inhibitors and calcium channel blockers for treating androgen-related conditions)
- IT 52-53-9, Verapamil 90-54-0, Etafenone 298-57-7, Cinnarizine 390-64-7, Prenylamine 2179-37-5, Bencyclane 2609-46-3, Amiloride 3416-26-0, Lidoflazine 6621-47-2, Perhexiline 13042-18-7, Fendiline 15793-40-5, Terodiline 16662-47-8, Gallopamil 21829-25-4, Nifedipine 22609-73-0, Niludipine 23031-25-6, Terbutaline 39562-70-4, Nitrendipine 42399-41-7, Diltiazem 52468-60-7, Flunarizine 55985-32-5, Nicardipine 62760-70-7, FR 7534 63675-72-9, Nisoldipine 64706-54-3, Bepridil 66085-59-4, Nimodipine 72509-76-3, Felodipine 72803-02-2, PY 108-068 75530-68-6, Nilvadipine 75695-93-1, Isradipine 77590-96-6, Flordipine 88150-42-9, Amlodipine 89964-00-1, Ryosidine 98319-26-7, Finasteride 116644-53-2, Mibefradil 164656-23-9 188754-67-8  
(combined use of 5 $\alpha$ -reductase inhibitors and calcium channel blockers for treating androgen-related conditions)
- IT 7440-70-2, Calcium, biological studies  
(combined use of 5 $\alpha$ -reductase inhibitors and calcium channel blockers for treating androgen-related conditions)

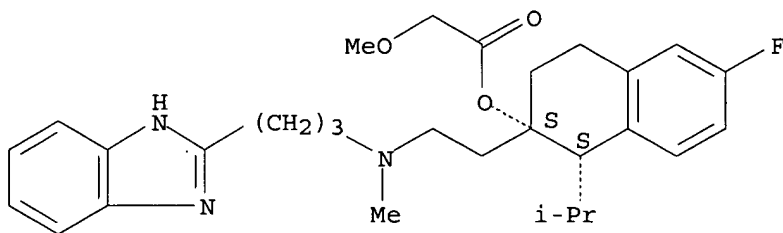
IT 9081-34-9, 5 $\alpha$ -Reductase  
(inhibitors; combined use of 5 $\alpha$ -reductase inhibitors and  
**calcium channel** blockers for treating  
androgen-related conditions)

IT 116644-53-2, Mibefradil  
(combined use of 5 $\alpha$ -reductase inhibitors and **calcium**  
**channel** blockers for treating androgen-related conditions)

RN 116644-53-2 USPATFULL

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 78 OF 198 USPATFULL on STN  
ACCESSION NUMBER: 89:15067 USPATFULL  
TITLE: Tetrahydronaphthalene derivatives as calcium antagonists  
INVENTOR(S): Branca, Quirico, Basel, Switzerland  
Jaunin, Roland, Basel, Switzerland  
Maki, Hans P., Basel, Switzerland  
Marti, Franzi, Riehen, Switzerland  
Ramuz, Henri, Birsfelden, Switzerland  
PATENT ASSIGNEE(S): Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4808605		19890228	<--
APPLICATION INFO.:	US 1987-119114		19871110 (7)	<--

	NUMBER	DATE	
PRIORITY INFORMATION:	CH 1986-4565	19861114	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Schwartz, Richard A.		
LEGAL REPRESENTATIVE:	Saxe, Jon S., Leon, Bernard S., Boxer, Matthew		
NUMBER OF CLAIMS:	21		
EXEMPLARY CLAIM:	19		
LINE COUNT:	2166		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds of the formula ##STR1## wherein R is lower-alkyl, R.sup.1 is halogen, R.sup.2 is C.sub.1 -C.sub.12 -alkyl, R.sup.3 is hydroxy, lower-alkoxy, lower-alkyl-carbonyloxy, lower-alkoxy-lower-alkylcarbonoyloxy, lower-alkylaminocarbonyloxy, arylaminocarbonyloxy or aryl-lower alkylaminocarbonyloxy, X is C.sub.1 -C.sub.18 -alkylene which optionally can be interrupted by 1,4-phenylene or interrupted or lengthened by 1,4-cyclohexylene, A is di- or tri-substituted

2-imidazolyl attached via an ethylene group or a substituted or unsubstituted heterocycle selected from the group consisting of benzimidazolyl, benzimidazolonyl, imidazo[4,5-c]pyridinyl, imidazo[4,5-c]pyridinonyl, benzthiazolyl, benzodiazepine-2,5-dion-1-yl and pyrrolo[2,1-c]-[1,4]benzodiazepine-5,11-dion-10-yl and n is the number 0 or 1, in the form of racemates and optical antipodes, as well as N-oxides and pharmaceutically usable acid addition salts thereof. The compounds of formula I have a pronounced calcium-antagonistic and anti-arrhythmic activity and can accordingly be used as medicaments, especially for the control or prevention of angina pectoris, ischaemia, arrhythmias, high blood pressure and cardiac insufficiency.

PI US 4808605 19890228 <--  
 AI US 1987-119114 19871110 (7) <--  
 PRAI CH 1986-4565 19861114 <--  
 ST heterocyclylalkylaminoethylnaphthalene prepn **cardiovascular**  
 agent; naphthalene heterocyclylalkylaminoethyl prepn  
**cardiovascular** agent; benzimidazole naphthylethylaminoalkyl prepn  
**cardiovascular** agent  
 IT **Ischemia**  
 (treatment of, [[(heterocyclylalkyl)amino]ethyl]naphthalenes for)  
 IT **Heart**, disease or disorder  
 (angina pectoris, treatment of, [[(heterocyclylalkyl)amino]et  
 hyl]naphthalenes for)  
 IT Ion channel blockers  
 (calcium, [[(heterocyclylalkyl)amino]ethyl]tetrahydronaphthal  
 enes)  
 IT **Heart**, disease or disorder  
 (failure, treatment of, [[(heterocyclylalkyl)amino]ethyl]tetrahydronaph  
 thalenes for)  
 IT 64137-52-6P 75937-12-1P 75950-19-5P 99230-20-3P 116643-69-7P  
 116643-70-0P 116643-71-1P 116643-74-4P 116643-75-5P 116643-76-6P  
 116643-77-7P 116643-78-8P 116643-79-9P 116643-80-2P 116643-81-3P  
 116643-82-4P 116643-85-7P 116643-86-8P 116643-88-0P 116643-89-1P  
 116643-91-5P 116643-92-6P 116643-98-2P 116643-99-3P 116644-19-0P  
 116644-20-3P 116644-21-4P 116644-22-5P 116644-25-8P 116644-26-9P  
 116644-27-0P 116644-28-1P 116644-29-2P 116644-33-8P 116644-34-9P  
 116644-36-1P 116644-37-2P 116644-38-3P 116644-40-7P 116644-41-8P  
 116644-44-1P 116644-45-2P 116644-46-3P 116644-47-4P 116644-55-4P  
 116644-56-5P 116666-61-6P 116666-62-7P 116666-85-4P 116666-86-5P  
 116666-87-6P 116666-88-7P 116666-94-5P 116666-95-6P 116666-96-7P  
 116666-97-8P 116666-98-9P 116666-99-0P 116667-00-6P 116667-01-7P  
 116667-04-0P 116667-05-1P 116667-06-2P 116667-07-3P 116667-11-9P  
 (preparation and reaction of, in preparation of **cardiovascular** agents)  
 IT 116643-63-1P 116643-64-2P 116643-65-3P  
 116643-66-4P 116643-67-5P 116643-68-6P 116643-72-2P  
 116643-73-3P 116643-83-5P 116643-84-6P 116643-87-9P  
 116643-90-4P 116643-94-8P 116643-96-0P 116643-97-1P  
 116644-00-9P 116644-01-0P 116644-02-1P  
 116644-04-3P 116644-05-4P 116644-06-5P  
 116644-07-6P 116644-08-7P 116644-09-8P  
 116644-10-1P 116644-11-2P 116644-12-3P 116644-13-4P 116644-14-5P  
 116644-15-6P 116644-16-7P 116644-17-8P 116644-18-9P  
 116644-23-6P 116644-24-7P 116644-31-6P  
 116644-32-7P 116644-35-0P 116644-39-4P 116644-42-9P  
 116644-43-0P 116644-48-5P 116644-49-6P 116644-50-9P  
 116644-51-0P 116644-52-1P 116644-53-2P 116644-54-3P  
 116666-60-5P 116666-63-8P 116666-64-9P 116666-65-0P  
 116666-67-2P 116666-69-4P 116666-71-8P 116666-73-0P 116666-75-2P  
 116666-76-3P 116666-77-4P 116666-78-5P  
 116666-79-6P 116666-80-9P 116666-81-0P 116666-82-1P

116666-83-2P 116666-84-3P 116666-89-8P 116666-90-1P  
 116666-91-2P 116666-92-3P 116666-93-4P  
 116667-02-8P 116667-03-9P 116667-08-4P 116667-09-5P  
 116667-10-8P

(preparation of, as **cardiovascular agent**)

IT 79-30-1, Isobutyryl chloride 95-54-5, 1,2-Benzenediamine, reactions  
 101-98-4 115-11-7, Isobutylene, reactions 137-07-5, 2-Aminothiophenol  
 2627-86-3 3128-07-2, 6-Oxoheptanoic acid 3415-35-8 3647-69-6  
 4048-33-3, 6-Amino-1-hexanol 5462-71-5 10040-98-9 16954-69-1  
 19500-95-9, Methoxyacetic anhydride 27687-12-3 38870-89-2,  
 Methoxyacetyl chloride 39650-73-2 39650-74-3 42042-68-2  
 50347-17-6, 6-(Methylamino)-1-hexanol 52099-72-6 55217-15-7  
 69891-92-5 78756-00-0 98008-66-3 104265-58-9 104265-59-0  
 116643-93-7 116643-95-9 116644-20-3 116644-30-5 116666-66-1  
 116666-68-3 116666-70-7 116666-72-9 116666-74-1

(reaction of, in preparation of **cardiovascular agents**)

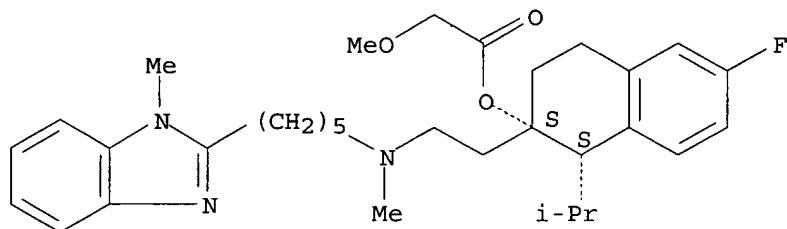
IT 116643-63-1P 116643-64-2P 116643-65-3P  
 116643-66-4P 116643-72-2P 116643-73-3P  
 116644-00-9P 116644-01-0P 116644-02-1P  
 116644-04-3P 116644-05-4P 116644-06-5P  
 116644-07-6P 116644-08-7P 116644-09-8P  
 116644-17-8P 116644-18-9P 116644-23-6P  
 116644-24-7P 116644-31-6P 116644-32-7P  
 116644-48-5P 116644-49-6P 116644-53-2P  
 116644-54-3P 116666-63-8P 116666-65-0P  
 116666-76-3P 116666-77-4P 116666-79-6P  
 116666-81-0P 116666-89-8P 116666-90-1P  
 116666-91-2P 116666-92-3P 116666-93-4P  
 116667-09-5P 116667-10-8P

(preparation of, as **cardiovascular agent**)

RN 116643-63-1 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-[2-[methyl[5-(1-methyl-1H-benzimidazol-2-yl)pentyl]amino]ethyl]-2-naphthalenyl ester, (1S-cis)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

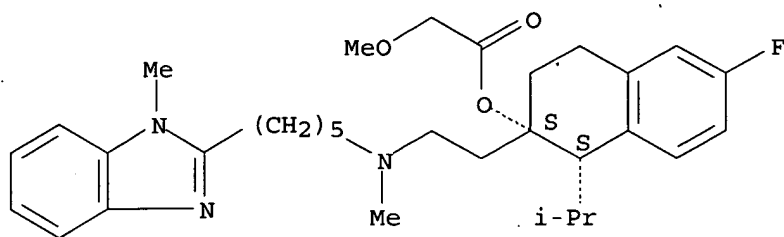


RN 116643-64-2 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-[2-[methyl[5-(1-methyl-1H-benzimidazol-2-yl)pentyl]amino]ethyl]-2-naphthalenyl ester, dihydrochloride, (1S-cis)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



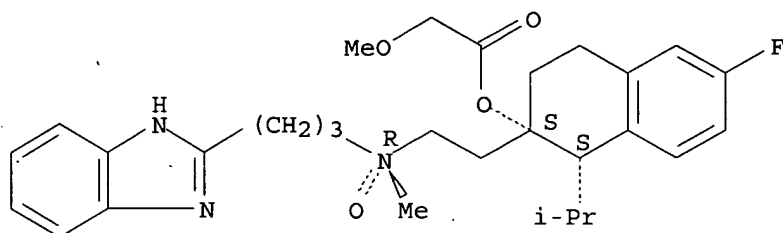


● 2 HCl

RN 116643-65-3 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methoxy]amino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, [1S-[1 $\alpha$ ,2 $\alpha$ ,2(S\*)]]- (9CI)  
(CA INDEX NAME)

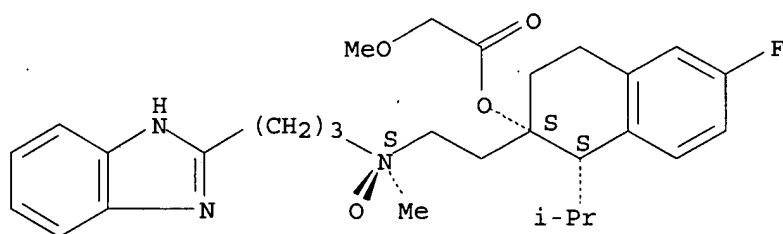
Absolute stereochemistry.



RN 116643-66-4 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methoxy]amino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, [1S-[1 $\alpha$ ,2 $\alpha$ ,2(R\*)]]- (9CI)  
(CA INDEX NAME)

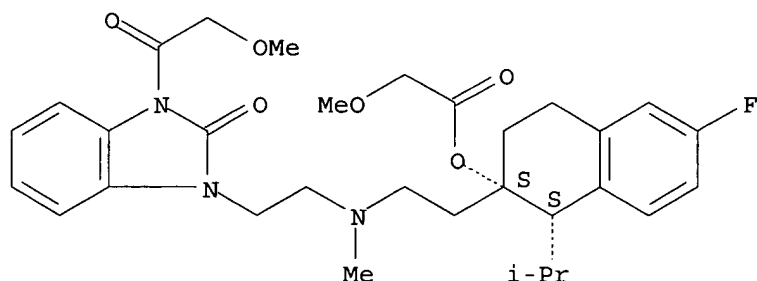
Absolute stereochemistry.



RN 116643-72-2 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[2-[[2,3-dihydro-3-(methoxyacetyl)-2-oxo-1H-benzimidazol-1-yl]ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, (1S-cis)- (9CI) (CA INDEX NAME)

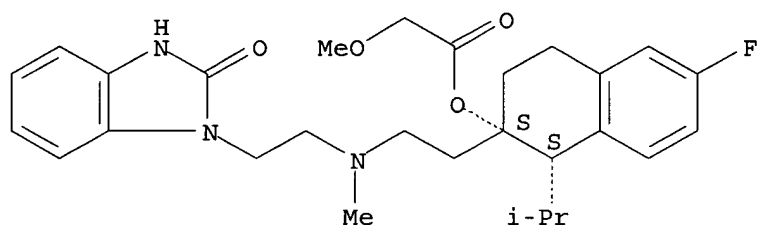
Absolute stereochemistry.



RN 116643-73-3 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[2-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, monohydrochloride, (1S-cis)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.

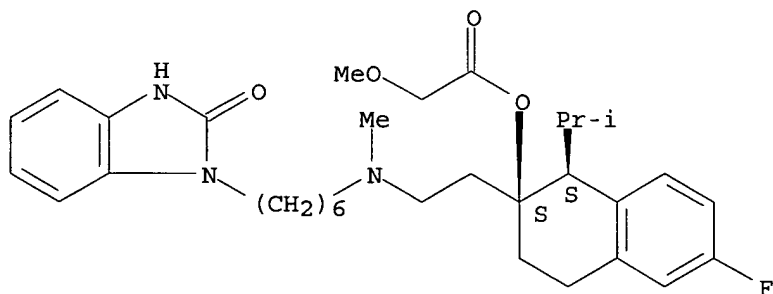


● HCl

RN 116644-00-9 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[6-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)hexyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, monohydrochloride, (1S-cis)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.

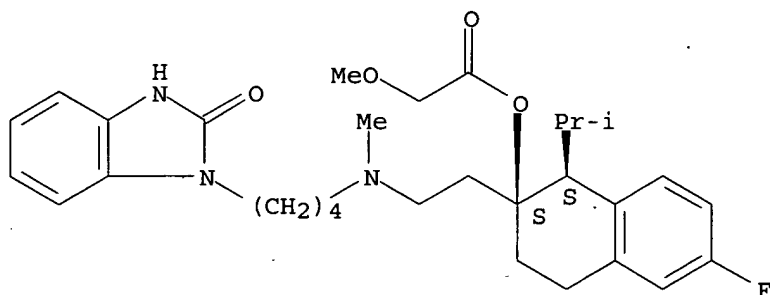


● HCl

RN 116644-01-0 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[4-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, monohydrochloride, (1S-cis)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.

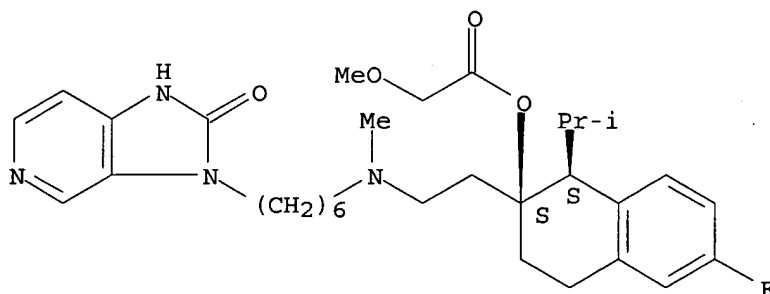


● HCl

RN 116644-02-1 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[6-(1,2-dihydro-2-oxo-3H-imidazo[4,5-c]pyridin-3-yl)hexyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride, (1S-cis)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 HCl

RN 116644-04-3 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-2-[2-[[4-[4-(1H-imidazol-1-yl)phenyl]butyl]methylamino]ethyl]-1-(1-methylethyl)-2-naphthalenyl ester, (1S-cis)-, ethanedioate (9CI) (CA INDEX NAME)

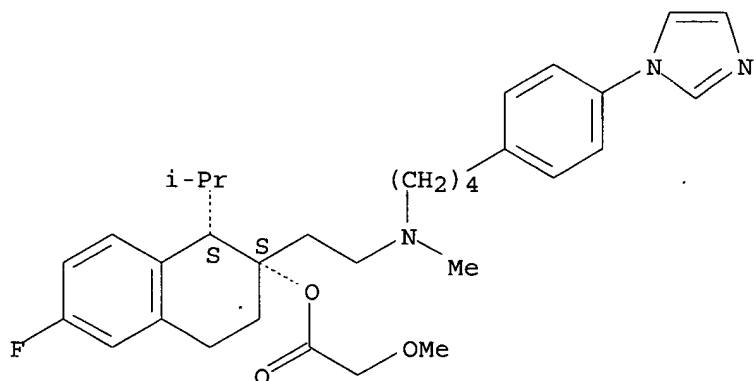
CM 1

CRN 116644-03-2

CMF C32 H42 F N3 O3

CDES 1:1S2:CIS

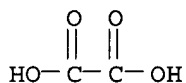
Absolute stereochemistry.



CM 2

CRN 144-62-7

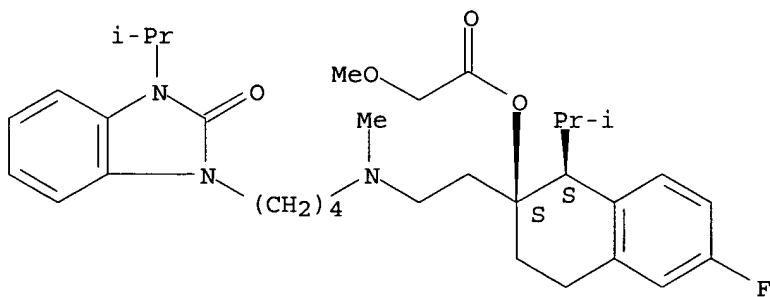
CMF C2 H2 O4



RN 116644-05-4 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[4-[2,3-dihydro-3-(1-methylethyl)-2-oxo-1H-benzimidazol-1-yl]butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, monohydrochloride, (1S-cis)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.



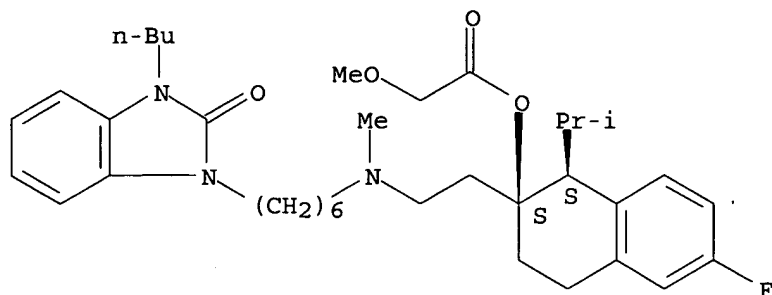
● HCl

RN 116644-06-5 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[6-(3-butyl-2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)hexyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, monohydrochloride, (1S-cis)- (9CI)

(CA INDEX NAME)

Absolute stereochemistry.

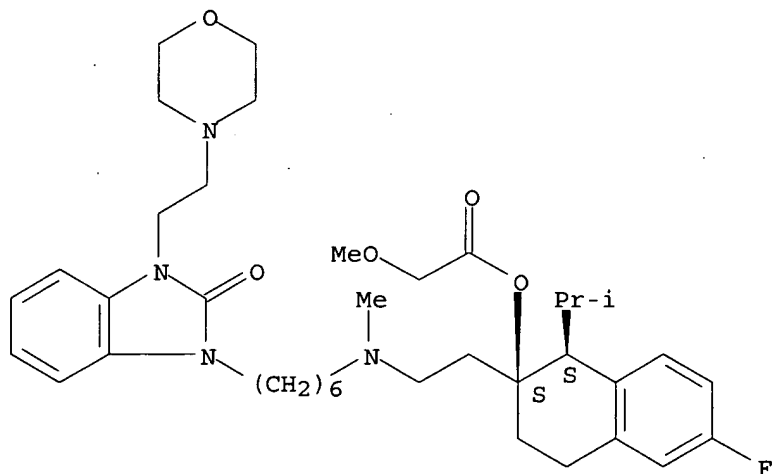


● HCl

RN 116644-07-6 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[6-[2,3-dihydro-3-[2-(4-morpholinyl)ethyl]-2-oxo-1H-benzimidazol-1-yl]hexyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride, (1S-cis)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

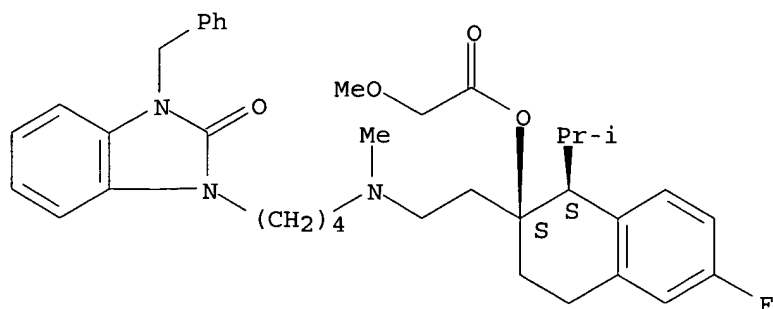


●2 HCl

RN 116644-08-7 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[4-[2,3-dihydro-2-oxo-3-(phenylmethyl)-1H-benzimidazol-1-yl]butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, monohydrochloride, (1S-cis)- (9CI) (CA INDEX NAME)

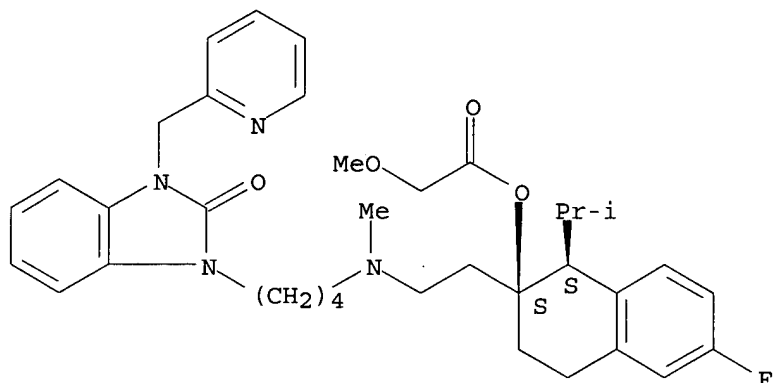
Absolute stereochemistry.



● HCl

RN 116644-09-8 USPATFULL  
 CN Acetic acid, methoxy-, 2-[2-[[4-[2,3-dihydro-2-oxo-3-(2-pyridinylmethyl)-1H-benzimidazol-1-yl]butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride, (1S-cis)- (9CI) (CA INDEX NAME)

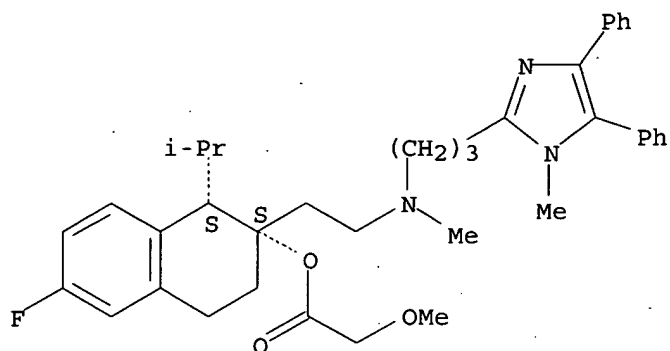
Absolute stereochemistry.



●2 HCl

RN 116644-17-8 USPATFULL  
 CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-[2-[methyl[3-(1-methyl-4,5-diphenyl-1H-imidazol-2-yl)propyl]amino]ethyl]-2-naphthalenyl ester, (1S-cis)- (9CI) (CA INDEX NAME)

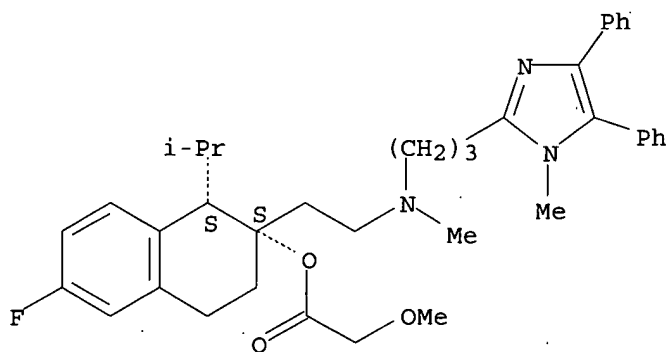
Absolute stereochemistry.



RN 116644-18-9 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-[2-[methyl[3-(1-methyl-4,5-diphenyl-1H-imidazol-2-yl)propyl]amino]ethyl]-2-naphthalenyl ester, dihydrochloride, (1S-cis)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

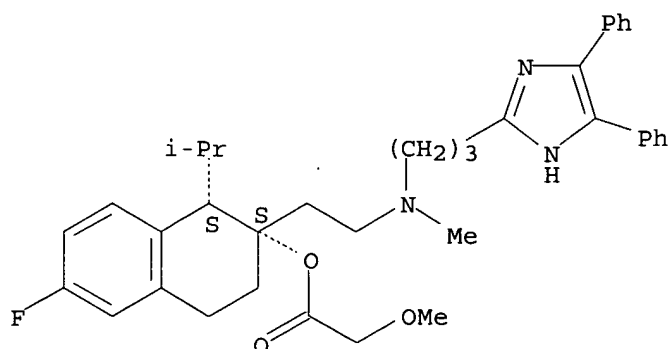


● 2 HCl

RN 116644-23-6 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[3-(4,5-diphenyl-1H-imidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride, (1S-cis)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

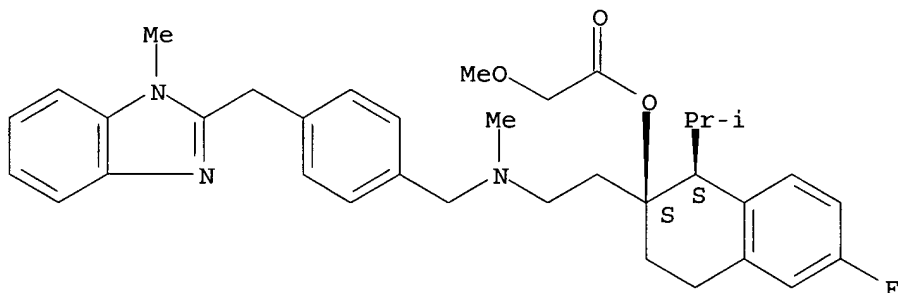


●2 HCl

RN 116644-24-7 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-[2-[methyl[[4-[(1-methyl-1H-benzimidazol-2-yl)methyl]phenyl]methyl]amino]ethyl]-2-naphthalenyl ester, dihydrochloride, (1S-cis)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

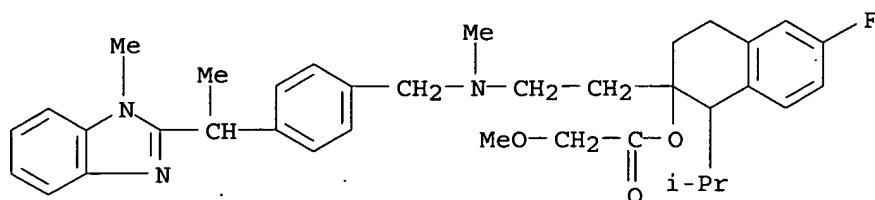


●2 HCl

RN 116644-31-6 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-[2-[methyl[[4-[1-(1-methyl-1H-benzimidazol-2-yl)ethyl]phenyl]methyl]amino]ethyl]-2-naphthalenyl ester, dihydrochloride (9CI) (CA INDEX NAME)



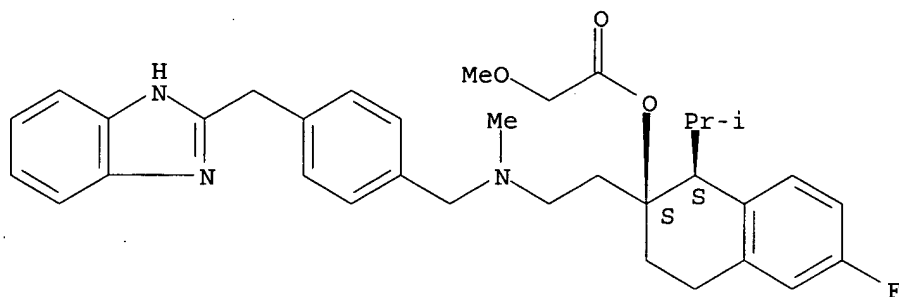


● 2 HCl

RN 116644-32-7 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[[4-(1H-benzimidazol-2-ylmethyl)phenyl]methyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride, (1S-cis)-(9CI)  
(CA INDEX NAME)

Absolute stereochemistry.

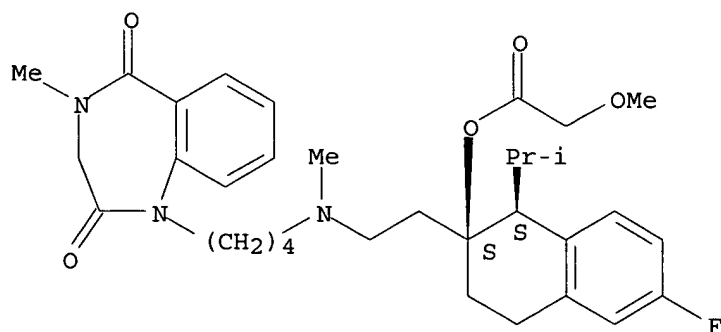


● 2 HCl

RN 116644-48-5 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-[2-[methyl[4-(2,3,4,5-tetrahydro-4-methyl-2,5-dioxo-1H-1,4-benzodiazepin-1-yl)butyl]amino]ethyl]-2-naphthalenyl ester, monohydrochloride, (1S-cis)-(9CI)  
(CA INDEX NAME)

Absolute stereochemistry.

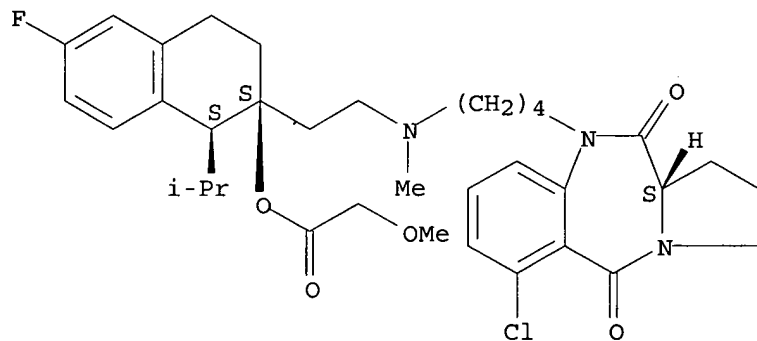


● HCl

RN 116644-49-6 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[4-(6-chloro-2,3,11,11a-tetrahydro-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-10(5H)-yl)butyl)methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, monohydrochloride, [1S-[1 $\alpha$ ,2 $\alpha$ ,2(R\*)]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

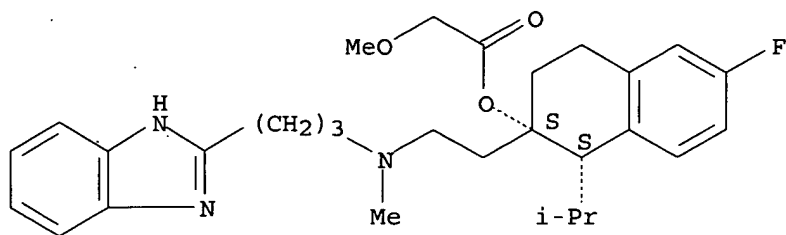


● HCl

RN 116644-53-2 USPATFULL

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[3-(1H-benzimidazol-2-yl)propyl)methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester (9CI) (CA INDEX NAME)

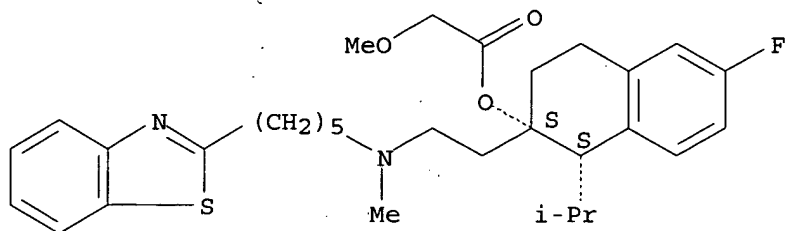
Absolute stereochemistry.



RN 116644-54-3 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[5-(2-benzothiazolyl)pentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, (1S-cis)- (9CI) (CA INDEX NAME)

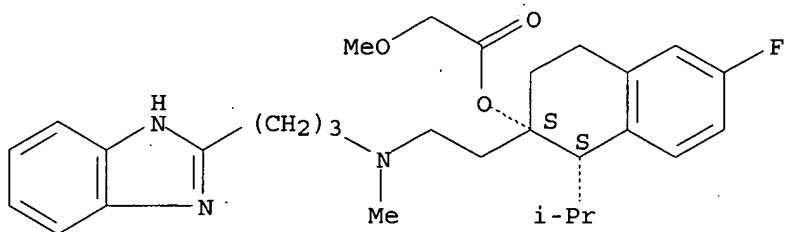
Absolute stereochemistry.



RN 116666-63-8 USPATFULL

CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

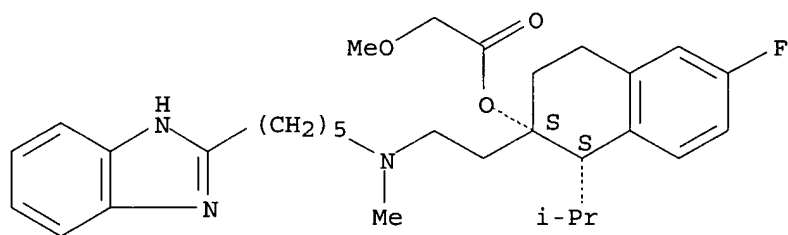


● 2 HCl

RN 116666-65-0 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[5-(1H-benzimidazol-2-yl)pentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride, (1S-cis)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

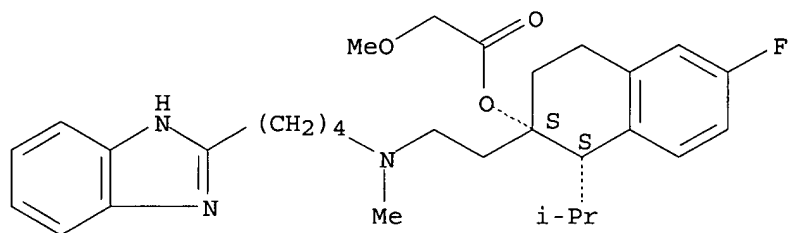


● 2 HCl

RN 116666-76-3 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[4-(1H-benzimidazol-2-yl)butyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride, (1S-cis)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

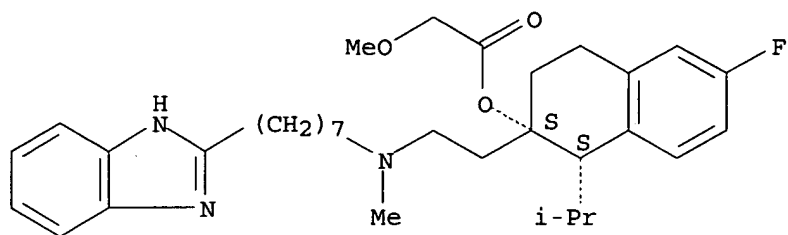


● 2 HCl

RN 116666-77-4 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[7-(1H-benzimidazol-2-yl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride, (1S-cis)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

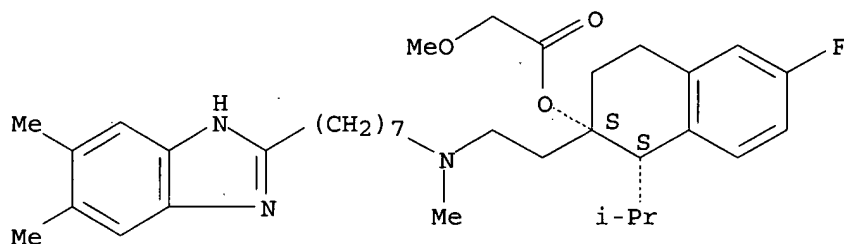


● 2 HCl

RN 116666-79-6 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[7-(5,6-dimethyl-1H-benzimidazol-2-yl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride, (1S-cis)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

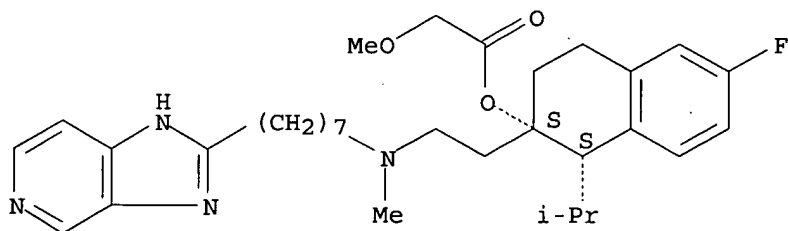


● 2 HCl

RN 116666-81-0 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-2-[2-[[7-(1H-imidazo[4,5-c]pyridin-2-yl)heptyl]methylamino]ethyl]-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride, (1S-cis)- (9CI) (CA INDEX NAME)

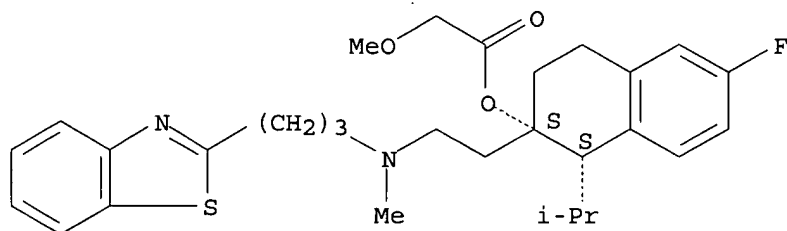
Absolute stereochemistry.



● 2 HCl

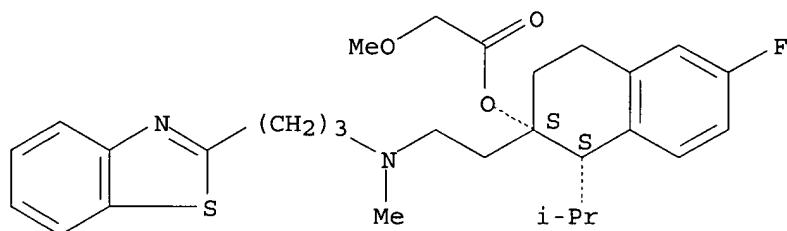
RN 116666-89-8 USPATFULL  
CN Acetic acid, methoxy-, 2-[2-[3-(2-benzothiazolyl)propyl]methylamino]ethyl  
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(1S-cis)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 116666-90-1 USPATFULL  
CN Acetic acid, methoxy-, 2-[2-[3-(2-benzothiazolyl)propyl]methylamino]ethyl  
]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester,  
dihydrochloride, (1S-cis)- (9CI) (CA INDEX NAME)

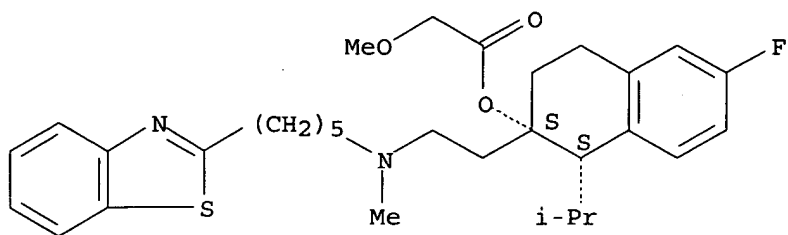
Absolute stereochemistry.



●2 HCl

RN 116666-91-2 USPATFULL  
CN Acetic acid, methoxy-, 2-[2-[5-(2-benzothiazolyl)pentyl]methylamino]ethyl  
]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester,  
dihydrochloride, (1S-cis)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

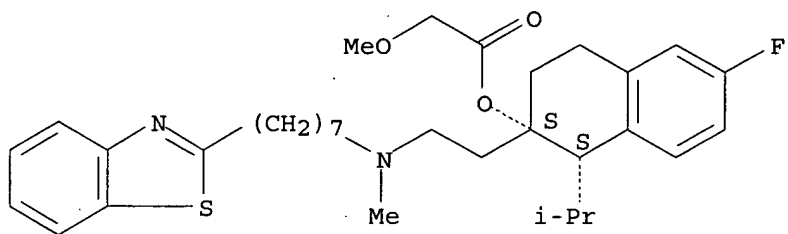


● 2 HCl

RN 116666-92-3 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[7-(2-benzothiazolyl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride, (1S-cis)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

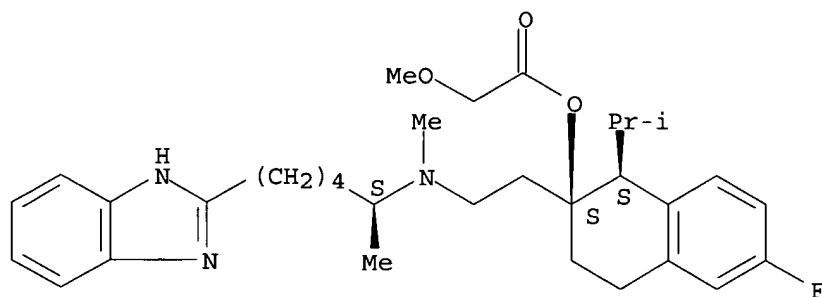


● 2 HCl

RN 116666-93-4 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[5-(1H-benzimidazol-2-yl)-1-methylpentyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride, [1S-[1 $\alpha$ ,2 $\alpha$ ,2(R\*)]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

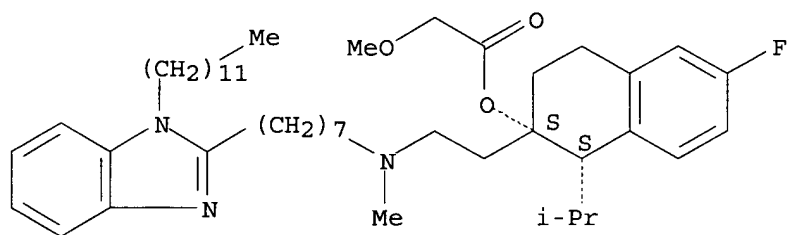


● 2 HCl

RN 116667-09-5 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[7-(1-dodecyl-1H-benzimidazol-2-yl)heptyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, dihydrochloride, (1S-cis)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



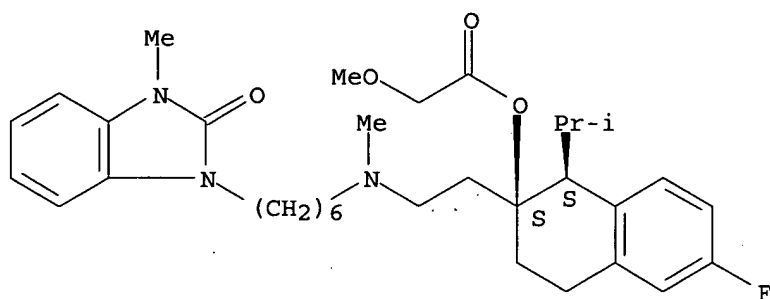
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RN 116667-10-8 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[6-(2,3-dihydro-3-methyl-2-oxo-1H-benzimidazol-1-yl)hexyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, monohydrochloride, (1S-cis)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.





● HCl

L103 ANSWER 79 OF 198    USPATFULL on STN  
 ACCESSION NUMBER:        87:50504    USPATFULL  
 TITLE:                    Tetrahydronaphthalene derivatives  
 INVENTOR(S):             Hengartner, Urs, Basel, Switzerland  
                              Ramuz, Henri, Birsfelden, Switzerland  
 PATENT ASSIGNEE(S):     Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S.  
                                                                                  corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4680310		19870714	<--
APPLICATION INFO.:	US 1985-786253		19851010 (6)	<--

	NUMBER	DATE	
PRIORITY INFORMATION:	CH 1984-4870	19841011	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Lone, Werren B.		
ASSISTANT EXAMINER:	Clarke, Vera C.		
LEGAL REPRESENTATIVE:	Saxe, Jon S., Leon, Bernard S., Boxer, Matthew		
NUMBER OF CLAIMS:	36		
EXEMPLARY CLAIM:	1,24		
LINE COUNT:	1305		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB     Tetrahydronaphthalene derivatives of the formula ##STR1## wherein Y, m, n, R and R.sup.1 to R.sup.9 are as set forth herein, are described.

These compounds have a pronounced calcium-antagonistic and anti-arrhythmic activity and can accordingly be used as medicaments, especially for the control or prevention of angina pectoris, ischaemia, arrhythmias and high blood pressure. The compounds of formula I can be prepared by the amination of a compound of the formula ##STR2## with a corresponding N-methyl-phenylalkylamine and optional subsequent O-acylation. Compounds of formula II and IV are also described and are within the scope of the invention.

PI	US 4680310	19870714	<--
AI	US 1985-786253	19851010 (6)	<--
PRAI	CH 1984-4870	19841011	<--
IT	<b>Ischemia</b>		
	(treatment of, aralkylaminoalkyltetrahydronaphthalenes for)		

IT **Heart, disease or disorder**  
**(angina pectoris, treatment of, aralkylaminoalkyltetrahydrona**  
**phthalenes for)**

IT 104204-56-0P 104204-57-1P 104204-58-2P 104204-59-3P 104204-60-6P  
104204-61-7P 104204-62-8P 104204-63-9P 104204-64-0P 104204-65-1P  
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```
(preparation of, as calcium antagonist)
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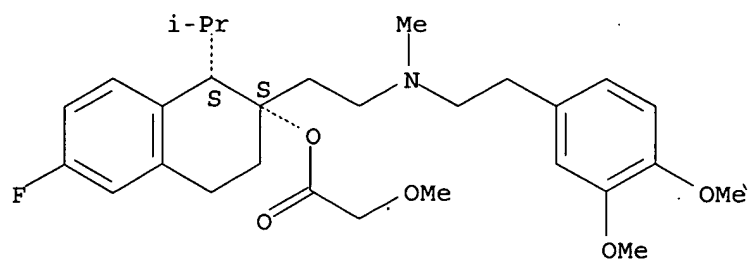
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**104205-32-5P 104205-33-6P 104205-34-7P**  
**104205-35-8P 104205-36-9P 104205-37-0P**  
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**104221-42-3P 104265-60-3P 104265-61-4P**  

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(preparation of, as calcium antagonist)
```

RN 104205-04-1 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, hydrochloride, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.

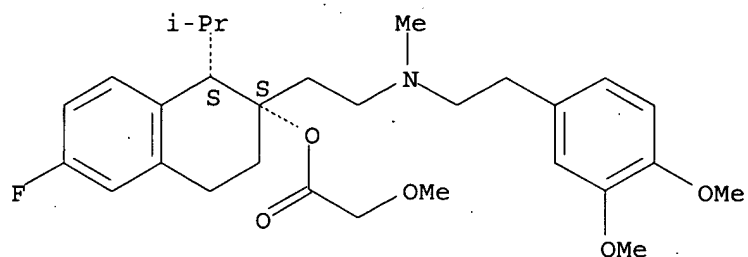


● HCl

RN 104205-05-2 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, cis- (9CI) (CA INDEX NAME)

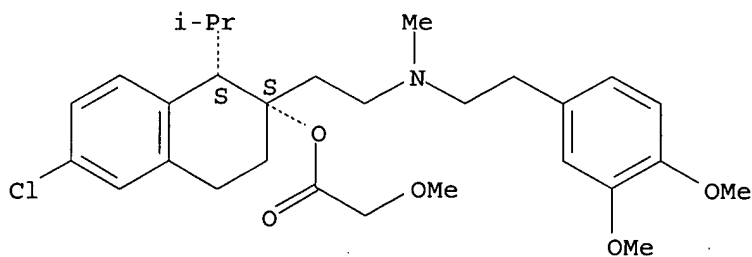
Relative stereochemistry.



RN 104205-06-3 USPATFULL

CN Acetic acid, methoxy-, 6-chloro-2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, cis- (9CI) (CA INDEX NAME)

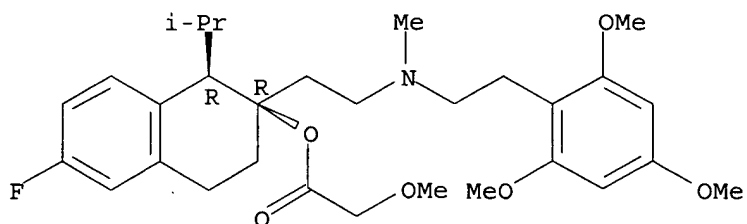
Relative stereochemistry.



RN 104205-15-4 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-[2-[methyl[2-(2,4,6-trimethoxyphenyl)ethyl]amino]ethyl]-2-naphthalenyl ester, hydrochloride, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.

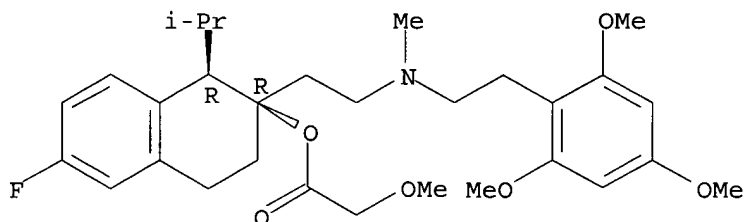


● HCl

RN 104205-16-5 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-[2-[methyl[2-(2,4,6-trimethoxyphenyl)ethyl]amino]ethyl]-2-naphthalenyl ester, cis- (9CI) (CA INDEX NAME)

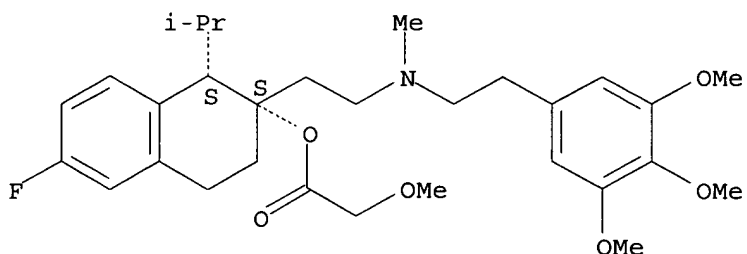
Relative stereochemistry.



RN 104205-17-6 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-[2-[methyl[2-(3,4,5-trimethoxyphenyl)ethyl]amino]ethyl]-2-naphthalenyl ester, hydrochloride, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.

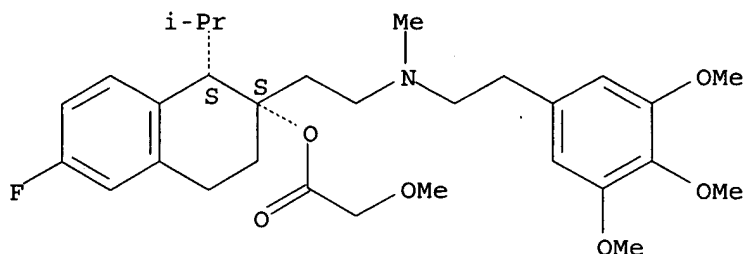


● HCl

RN 104205-18-7 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-[2-[methyl[2-(3,4,5-trimethoxyphenyl)ethyl]amino]ethyl]-2-naphthalenyl ester, cis- (9CI) (CA INDEX NAME)

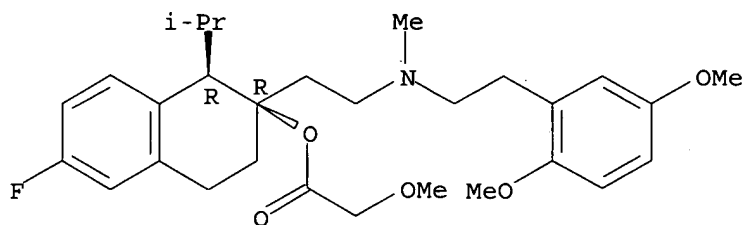
Relative stereochemistry.



RN 104205-19-8 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[2-(2,5-dimethoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, hydrochloride, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.

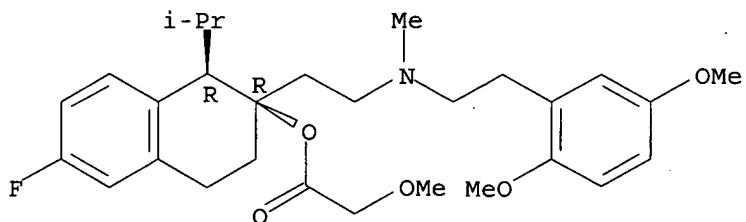


● HCl

RN 104205-20-1 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[2-(2,5-dimethoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, cis- (9CI) (CA INDEX NAME)

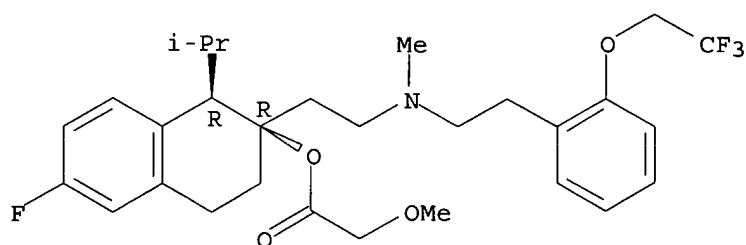
Relative stereochemistry.



RN 104205-21-2 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-[2-[methyl[2-[2-(2,2,2-trifluoroethoxy)phenyl]ethyl]amino]ethyl]-2-naphthalenyl ester, hydrochloride, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.

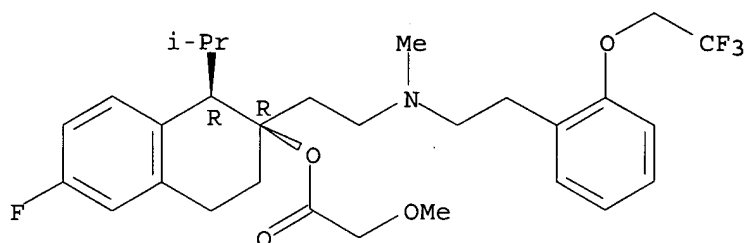


● HCl

RN 104205-22-3 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-[2-[methyl[2-[2-(2,2,2-trifluoroethoxy)phenyl]ethyl]amino]ethyl]-2-naphthalenyl ester, cis- (9CI) (CA INDEX NAME)

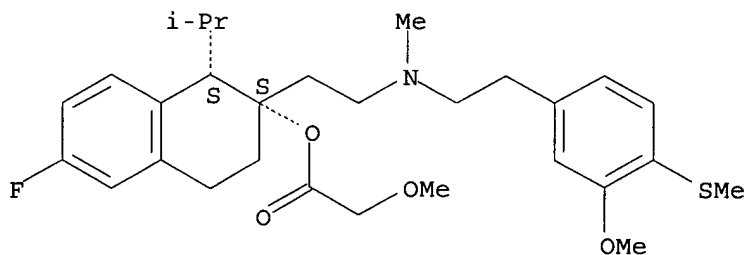
Relative stereochemistry.



RN 104205-23-4 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-2-[2-[[2-[3-methoxy-4-(methylthio)phenyl]ethyl]methylamino]ethyl]-1-(1-methylethyl)-2-naphthalenyl ester, hydrochloride, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.

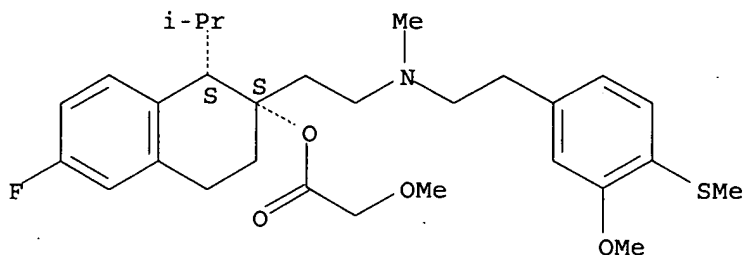


● HCl

RN 104205-24-5 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-2-[2-[[2-[3-methoxy-4-(methylthio)phenyl]ethyl]methylamino]ethyl]-1-(1-methylethyl)-2-naphthalenyl ester, cis- (9CI) (CA INDEX NAME)

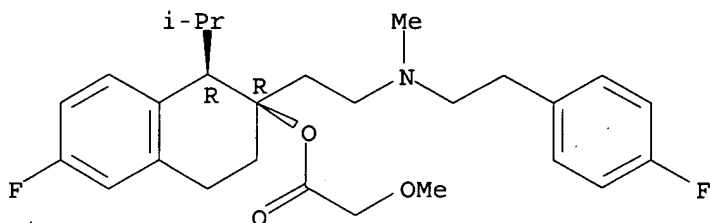
Relative stereochemistry.



RN 104205-25-6 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-2-[2-[[2-(4-fluorophenyl)ethyl]methylamino]ethyl]-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, hydrochloride, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.

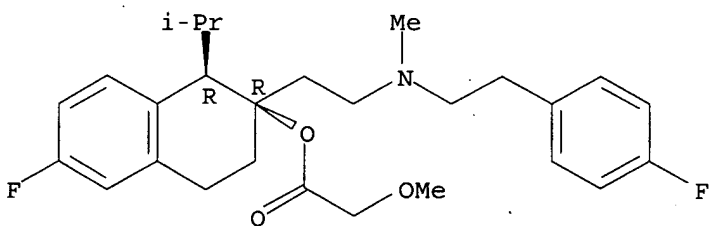


● HCl

RN 104205-26-7 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-2-[2-[[2-(4-fluorophenyl)ethyl]methylamino]ethyl]-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, cis- (9CI) (CA INDEX NAME)

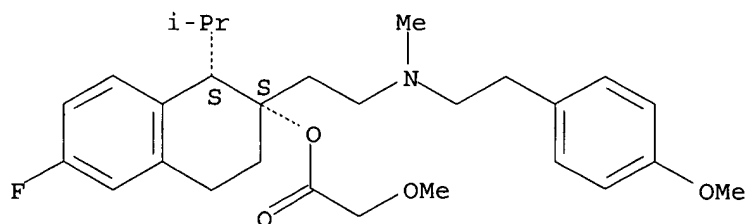
Relative stereochemistry.



RN 104205-28-9 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-2-[2-[[2-(4-methoxyphenyl)ethyl]methylamino]ethyl]-1-(1-methylethyl)-2-naphthalenyl ester, cis- (9CI) (CA INDEX NAME)

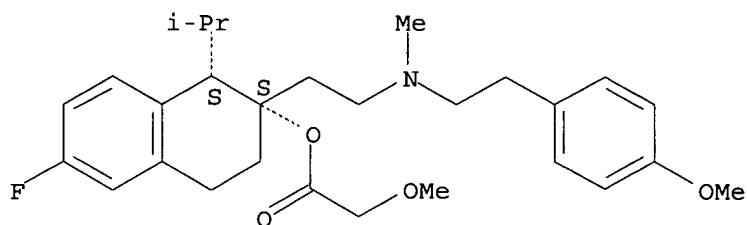
Relative stereochemistry.



RN 104205-30-3 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-2-[2-[[2-(4-methoxyphenyl)ethyl]methylamino]ethyl]-1-(1-methylethyl)-2-naphthalenyl ester, hydrochloride, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.

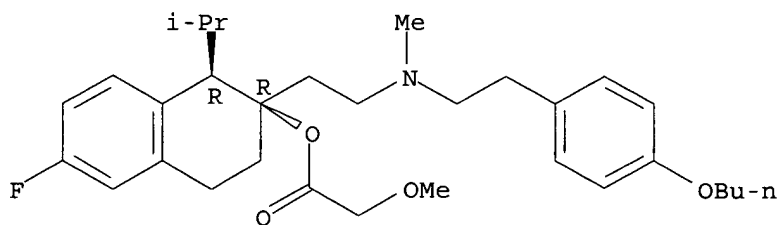


● HCl

RN 104205-31-4 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[2-(4-butoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, hydrochloride, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.



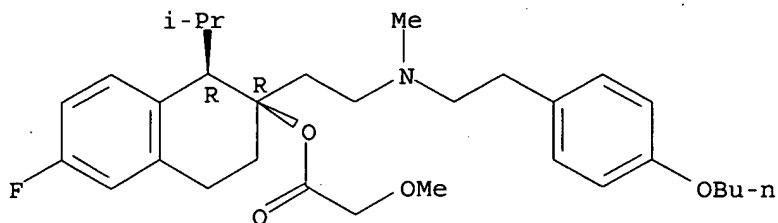
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RN 104205-32-5 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[2-(4-butoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.

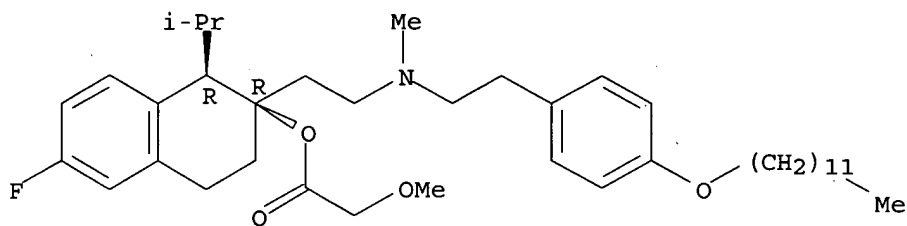




RN 104205-33-6 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[2-[4-(dodecyloxy)phenyl]ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, hydrochloride, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.

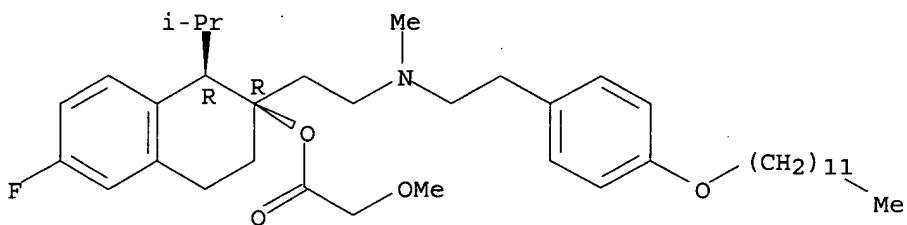


● HCl

RN 104205-34-7 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[2-[4-(dodecyloxy)phenyl]ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, cis- (9CI) (CA INDEX NAME)

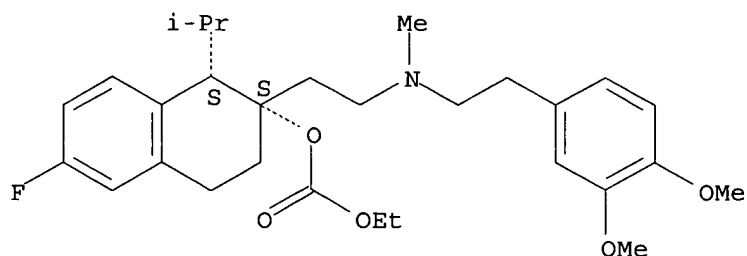
Relative stereochemistry.



RN 104205-35-8 USPATFULL

CN Carbonic acid, 2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ethyl ester, hydrochloride, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.

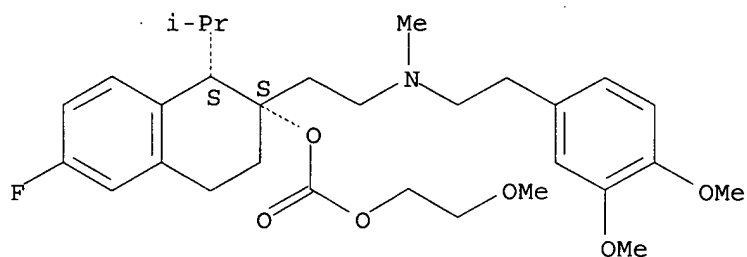


● HCl

RN 104205-36-9 USPATFULL

CN Carbonic acid, 2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl 2-methoxyethyl ester, hydrochloride, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.

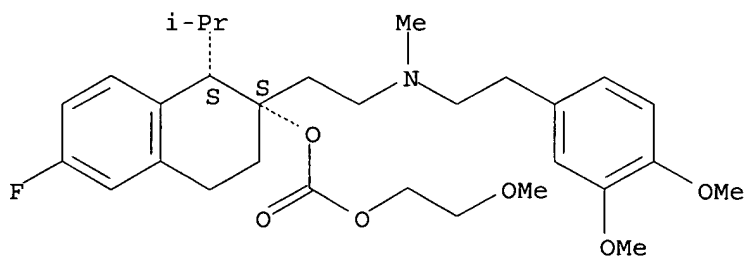


● HCl

RN 104205-37-0 USPATFULL

CN Carbonic acid, 2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl 2-ethoxyethyl ester, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.

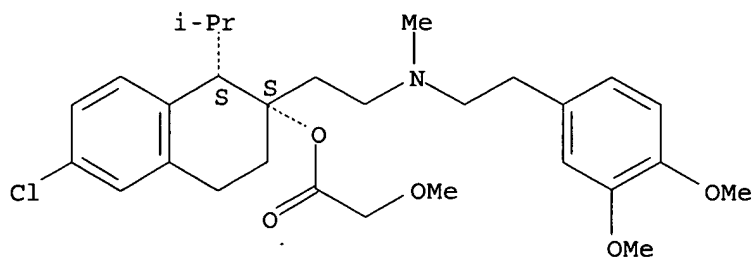


RN 104221-39-8 USPATFULL

CN Acetic acid, methoxy-, 6-chloro-2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, hydrochloride, cis- (9CI) (CA INDEX NAME)

NAME)

Relative stereochemistry.

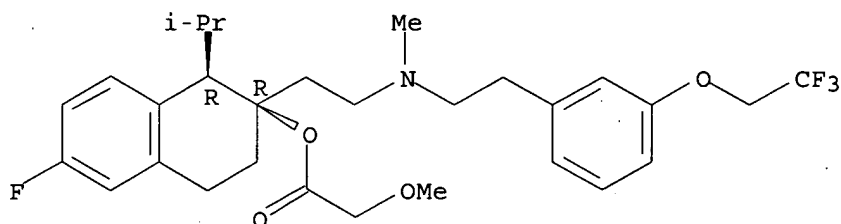


● HCl

RN 104221-40-1 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-[2-[methyl[2-[3-(2,2,2-trifluoroethoxy)phenyl]ethyl]amino]ethyl]-2-naphthalenyl ester; hydrochloride, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.

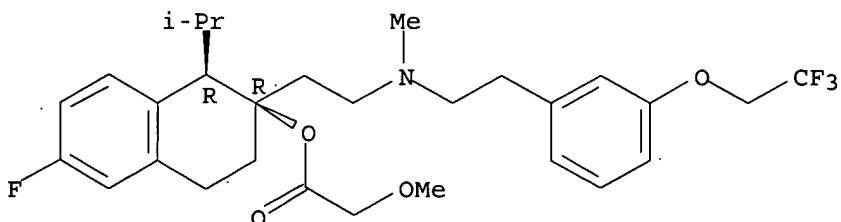


● HCl

RN 104221-41-2 USPATFULL

CN Acetic acid, methoxy-, 6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-[2-[methyl[2-[3-(2,2,2-trifluoroethoxy)phenyl]ethyl]amino]ethyl]-2-naphthalenyl ester, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.

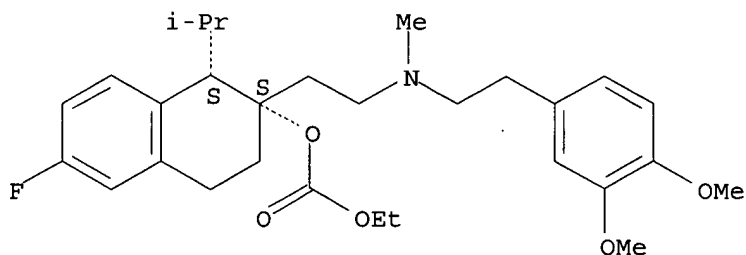


RN 104221-42-3 USPATFULL

CN Carbonic acid, 2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ethyl ester,

cis- (9CI) (CA INDEX NAME)

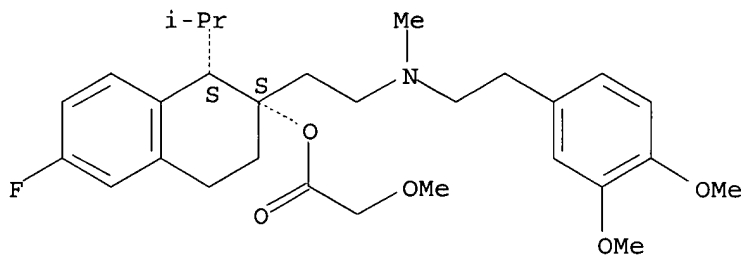
Relative stereochemistry.



RN 104265-60-3 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, hydrochloride, (1S-cis)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

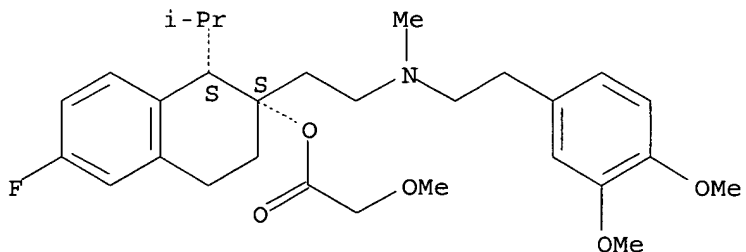


● HCl

RN 104265-61-4 USPATFULL

CN Acetic acid, methoxy-, 2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, (1S-cis)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=&gt; diall abeq tech abex 80-85

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, TOXCENTER, MEDLINE, BIOSIS, PASCAL, DRUGU, SCISEARCH, EMBASE, WPIX' - CONTINUE? (Y)/N:y

L103 ANSWER 80 OF 198 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 2003-075655 [07] WPIX  
 DOC. NO. CPI: C2003-019682  
 TITLE: Use of new and known probucol monoester compounds for increasing high density lipoprotein cholesterol level used for treating cardiovascular diseases.  
 DERWENT CLASS: B05  
 INVENTOR(S): LUCHOOMUN, J; SAXENA, U; SIKORSKI, J A; SUNDELL, C L  
 PATENT ASSIGNEE(S): (LUCH-I) LUCHOOMUN J; (SAXE-I) SAXENA U; (SIKO-I) SIKORSKI J A; (SUND-I) SUNDELL C L; (ATHE-N) ATHEROGENICS INC  
 COUNTRY COUNT: 101  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
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W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK							
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR							
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT							
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ZW							
US 2003064967	A1	20030403	(200325)			A61K031-66	
EP 1385501	A2	20040204	(200410)	EN		A61K031-225	
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RO SE SI TR							
AU 2002320025	A1	20021111	(200433)			A61K031-00	
JP 2005508850	W	20050407	(200524)		107	A61K031-235	
US 2005065121	A1	20050324	(200526)			A61K031-66	

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002087556	A2	WO 2002-US12678	20020411
US 2003064967	A1 Provisional	US 2001-283376P	20010411 <--
	Provisional	US 2001-345025P	20011109 <--
		US 2002-122516	20020411
EP 1385501	A2	EP 2002-749523	20020411
		WO 2002-US12678	20020411
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JP 2005508850	W	JP 2002-584902	20020411
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	Cont of	US 2002-122516	20020411
		US 2004-977752	20041029

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1385501	A2 Based on	WO 2002087556
AU 2002320025	A1 Based on	WO 2002087556
JP 2005508850	W Based on	WO 2002087556

PRIORITY APPLN. INFO: **US 2001-345025P****20011109; US****2001-283376P****20010411;**

US 2002-122516

20020411; US

2004-977752

20041029

## INT. PATENT CLASSIF.:

MAIN: A61K031-00; A61K031-225; A61K031-235; A61K031-66  
SECONDARY: A61K031-138; A61K031-198; A61K031-216; A61K031-22;  
A61K031-255; A61K031-275; A61K031-397; A61K031-40;  
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A61K031-517; A61K031-55; A61K031-554; A61K031-575;  
A61K045-00; A61P003-06; **A61P009-10**; C07C323-21

## BASIC ABSTRACT:

WO 200287556 A UPAB: 20030129

NOVELTY - Use of probucol monoester compounds (I) and (II) is claimed for increasing high density lipoprotein (HDL) cholesterol level or improving the functionality of circulating HDL.

DETAILED DESCRIPTION - Use of probucol monoester compounds of formula T-linker-X (I) and T-linkera-O-SO<sub>2</sub>-OR<sub>4</sub> (II), their salts or prodrugs is claimed for increasing high density lipoprotein (HDL) cholesterol level or improving the functionality of circulating HDL.

T = a group of formula (i);

linker = (CH<sub>2</sub>)<sub>g</sub>Q(CH<sub>2</sub>)<sub>h</sub>;

linkera = (CH<sub>2</sub>)<sub>k</sub>, alkyl, lower alkyl, alkenyl, alkynyl, heterocyclyl, aryl, heteroaryl, aralkyl, heterocyclylalkyl, heteroarylalkyl, alkaryl, alkylheterocyclyl or alkylheteroaryl (all optionally substituted by at least one OH, alkyl, lower alkyl, 1-5C alkoxy, halo, NO<sub>2</sub>, amino, CN, aminocarbonyl, alkylamino or halo(1-5C)alkyl);

g = 1-3;

h = 0-3;

k = 1-10;

Q = O, S or CH<sub>2</sub>;X = CH<sub>2</sub>COOR, COOR or CONR<sub>1</sub>R<sub>2</sub>;

R, R<sub>1</sub>, R<sub>2</sub> = H, alkyl, lower alkyl, aryl, aralkyl or alkaryl (all optionally substituted by at least one OH, halo, alkoxy, carboxy or amino), or

R<sub>1</sub> + R<sub>2</sub> = 4-8 membered ring;

R<sub>4</sub> = H, alkyl, lower alkyl, alkenyl, alkynyl, heterocyclyl, aryl, heteroaryl, aralkyl, heterocyclylalkyl, heteroarylalkyl, alkaryl, alkylheterocyclyl or alkylheteroaryl (all optionally substituted by at least one OH, alkyl, lower alkyl, 1-5C alkoxy, halo, NO<sub>2</sub>, amino, CN, aminocarbonyl, alkylamino or halo(1-5C)alkyl).

INDEPENDENT CLAIMS are also included for the following:

(1) new compounds (II), and;

(2) measuring the ability of a compound (preferably probucol monoester) to increase the level of circulating HDL cholesterol which comprises administering the compound to an animal (preferably mouse or hamster) transfected with the human apo A-1 gene and measuring the increase in human apo A-1 HDL.

ACTIVITY - Cardiant; Antiarteriosclerotic.

MECHANISM OF ACTION - None given in the source material.

USE - Used for increasing HDL cholesterol level, improving the circulating functionality of HDL and treating cardiovascular diseases e.g. atherosclerosis.

In an in vitro cell culture assay, HepG2 cells were cultured in minimum essential medium containing 10% FBS, and streptomycin (100 mu g/ml), penicillin (100 unit/ml) and glutamine (4 mM). Cells were grown for 2 days till they were 80% confluent in 6-well or 12-well plates before

studies. To measure apoAI, 96-well microtiter plates were coated with a 1:1000 diluted mixture of three monoclonal antibodies against human apoAI for 2 hours and incubated in succession with HDL3 (0 - 15 ng/well), carboxymethoxyacetic acid, mono(4-(1-((3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl)thio)-1-methyl-ethyl)-thio-2,6-bis(1,1-dimethylethyl)phenyl)ester (Ib) (test compound)/probucol (control compound), sheep polyclonal anti-apoAI serum, alkaline phosphatase-labeled rabbit anti-sheep and para-nitrophenyl phosphate (1 mg/ml in 10 mmol/l ethanolamine, 0.5 mmol/L MgCl<sub>2</sub>, pH 9.5), for 2, 1 and 1 hour respectively at 37 deg. C. The plates were washed three times between different incubations. The percentage increase apoAI HDL in HepG2 cells using the test compound/control compound was 47/-21.

**ADVANTAGE** - The probucol monoesters increase the (HDL-c) level and improve the functionality of circulating high density lipoprotein in a host, by increasing HDL-particle affinity for hepatic cell surface receptors or increasing the half life of apoAI-HDL by at least 20 (preferably 30, 40, 50 or 60)% without increasing serum LDLc levels or decreasing apoAI protein synthesis. The medicament increases the HDL holoprotein levels by decreasing the internalization and degradation of HDL holoproteins.

Dwg.0/7

**FILE SEGMENT:** CPI  
**FIELD AVAILABILITY:** AB; GI; DCN  
**MANUAL CODES:** CPI: B01-C04; B01-D02; B03-H; B06-A01; B06-D01; B06-D11; B07-A02A; B07-A02B; B07-D04C; B07-D08; B07-D09; B07-D13; B10-A08; B10-A09A; B10-A13C; B10-A13D; B10-A15; B10-A17; B10-B03B; B10-C03; B14-F01; B14-F07

**TECH** UPTX: 20030129

**TECHNOLOGY FOCUS - ORGANIC CHEMISTRY** - Preparation: No general preparation of (II) is given in the source material.

**TECHNOLOGY FOCUS - PHARMACEUTICALS** - Preferred Compounds: The method also comprises administering a statin comprising lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, mevastatin, velostatin, compactin, dalvastatin, fluindostatin, dihydrocompactin, rivastatin, SDZ-63,370, CI-981, HR-780, L-645,164, CL-274,471, alpha, beta and gamma tocotrienol, (3R,5S,6E)-9,9-bis(4-fluorophenyl)-3,5-dihydroxy-8-(1-methyl-1H-tetrazol-5-yl)-6,8-nonadienoic acid, L-arginine salt, (S)-4-((4-(4-fluorophenyl)-5-methyl-2-(1-methylethyl)-6-phenyl-3-pyridinyl)ethenyl)-hydroxy-phosphinyl)-3-hydroxy-butanoic acid, disodium salt, BB-476, (British biotechnology), dihydrocompactin, (4R-(4-alpha, 6beta(E))) -6-(2-(5-(4-fluorophenyl)-3-(1-methylethyl)-1-(2-pyridinyl)-1H-pyrazol-4-yl)ethenyl)tetrahydro-4-hydroxy-2H-pyran-2-one or 1H-pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-((phenylamino)carbonyl)-calcium salt(R-(Rasterisk,Rasterisk)).

The method also comprises administering a fibric acid derivative comprising clofibrate, fenofibrate, ciprofibrate, bezafibrate or gemfibrozil.

The method also comprises administering a saturated phytosterol or stanol comprising campestanol, cholestanol, clionastanol, coprostanol, 22,23-dihydro-brassicastanol, epicholestanol, fucostanol or stigmastanol.

The method also comprises administering a diuretic comprising hydrochlorothiazide, chlorothiazide, furosemide, bumetanide, ethacrynic acid, amiloride, triameterene, spironolactone, eplerenone, acetazolamide, althiazide, amanozine, ambuside, amiloride, arbutin, azosemide, bendroflumethiazide, benzthiazide, benzylhydro-chlorothiazide, butazolamide, buthiazide, chloraminophenamide, chlorazanyl, chlorthalidone, clofenamide, clopamide, clorexolone, cyclopenthiazide, cyclothiazide, disulfamide, epithiazide, ethiazide, ethoxolamide,

etozolin, fenquizone, furosemide, hydracarbazine, hydrochlorothiazide, hydroflumethiazide, indapamide, isosorbide, mannitol, mefruside, methazolamide, methyclothiazide, meticrane, metochalcone, metolazone, muzolimine, paraflutizide, perhexiline, piretanide, polythiazide, quinethazone, teclothiazide, ticrynafen, torasemide, triamterene, trichlormethiazide, tripamide, urea or xipamide.

The method also comprises administering an antihypertensive agent comprising an andrenergic blocker, a mixed alpha/beta andrenergic blocker, an alpha andrenergic blocker, beta andrenergic blocker, an andrenergic stimulant, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, a **calcium channel**

blocker, a diuretic or a vasodilator. The andrenergic blocker comprises phenoxybenzamine, guanadrel, guanethidine, reserpine, terazosin, prazosin or polythiazide. The andrenergic stimulant comprises methyl dopa, methyl dopate, clonidine, chlorthalidone, guanfacine, guanabenz or trimethaphan. The alpha/beta andrenergic blocker comprises carvedilol or labetalol. The beta andrenergic blocker comprises propranolol, metaprolol, acebutol, alprenol, amosulal, arotinolol, atenolol, befunolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucumolol, bufetolol, bufuralol, bunitrolol, buprandolol, butiridine hydrochloride, ebutofilolol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, cloranolol, dilevalol, epanolol, indenolol, labetalol, levobunolol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivalol, nipradilol, oxprenolol, perbutolol, pindolol, practolol, pronethalol, propanolol, sotalol, sufinalol, talindol, tertatolol, tilisolol, timolol, toliprolol or xibenolol. The alpha andrenergic blocker comprises doxazosin and phentolamine, amosulalol, arotinolold, apiprazole, doxazosin, fenspiride, indoramin, labetalol, naftopidil, nicergoline, prazosin, tamsulosin, tolazoline, trimazosin or yohimbine. The angiotensin converting enzyme inhibitor comprises quinapril, perindopril, erbumine, ramipril, captopril, fosinopril, trandolapril, lisinopril, moexipril, enalapril, benazepril, alacepril, ceronapril, delapril, imadapril, moveltopril, spirapril or temocapril. The angiotensin II receptor antagonist comprises candesartan cilexetil, inbesartan, losartan, valsartan or eprosartan.

The **calcium channel** blocker comprises verapamil, diltiazem, nifedipine, nimodipine, delodipine, nicardipine, isradipine, amlodipine, bepridil, clentiazem, fendiline, gallopamil, **mibefradil**, prenylamine, semotiadil, terodiline, verapamil, aranipine, bamidipine, benidipine, cilnidipine, efonidipine, elgodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone or perhexiline. The vasodilator comprises hydralazine, minoxidil, diazoxide, nitroprusside, aluminum nicotinate, amotriphene, bamethan, bencyclane, bendazol, benfurodil hemisuccinate, benziadarone, betahistine, bradykinin, bovincamine, bufeniode, buflomedil, butalamine, cetiedil, chloracizine, chromonar, ciclonicate, cinepazide, cinnarizine, citicoline, clobenfuril, clonitrate, cloricromen, cycandelate, diisopropylamine dichloroacetate, dilazep, dipyrindamole, droprenilamine, ebumamonine, efloxate, eledoisin, erythrityl, etafenone, fasudil, fendiline, fenoxedil, floredil, flunarizine, ganglefene, hepronicate, hexesterol, hexobendine, ibudilast, ifenprodil, iloprost, inositol, isoxsuprine, itramin tosylate, kallidin, kallikrein, khellin, lidofiazine, lomerizine, mannitol, hexanitrate, medibazine, moxislyte, nafronyl, nicametate, nicergoline, nicofuranose, nimodipine, nitroglycerin, nyldrin, papaverine, pentaerythritol tetranitrate, pentifylline, pentoxifylline, pentrinitrol, perhexilline, pimefylline, piribedil, prenylamine, propatyl nitrate, prostaglandin EI, suloctidil, tinofedrine, tolazoline, trapidil, tricromyl, trimetazidine, trolnitrate



phosphate, vincamine, vinpocetine, viquidil, visnadine or xanthinol niacinate.

The method also comprises administering a cholesteryl ester transfer protein inhibitor comprising (-)-(2R,4S)-4-amino-2,2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester.

ABEX UPTX: 20030129

SPECIFIC COMPOUNDS - The use of four compounds (I) i specifically claimed e.g:

pentanedioic acid, mono(4-((1-((3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl)thio)-1-methylethyl)thio)-2,6-bis(1,1-dimethylethyl)phenyl)ester (Ia).

One compound (II) is specifically claimed i.e:

4-(4-(1-((3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl)thio)-1-methylethyl)thio-2,6-bis(1,1-dimethylethyl)phenoxy)-4-oxo-1-butyl sodium sulfate (IIa).

ADMINISTRATION - The dosage is 0.1-500 (preferably 1-100) mg/kg/day orally, parenterally (including intravenously, intradermally or subcutaneously) or topically.

EXAMPLE - (4-((1-((3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl)thio)-1-methylethyl)thio)-2,6-bis(1,1-dimethylethyl)phenyl)-4-hydroxybutyrate (12.5 g) and sulfur trioxide trimethylamine complex (12.5 g) were dissolved in dimethylformamide (150 ml) and stirred at room temperature for 2 hours. It was evaporated under vacuum to give a residue which was dissolved in dichloromethane (100 ml). The solution was washed with water (2 x 30 ml) and evaporated. Chromatography (dichloromethane/methanol, 10:1, 5:1) gave 3-(4-((1-((3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl)thio)-1-methylethyl)thio)-2,6-bis(1,1-dimethylethyl)phenoxy)propyl hydrogen sulfate.

Tetrahydrofuran (200 ml) was added to this compound, sodium hydroxide (0.8 g) in water (5 ml) was added and the mixture was stirred at room temperature for 2 hours. It was evaporated and then 1N NaOH (200 ml) was added and the mixture stirred for 30 minutes. The precipitate was filtered out and dried to give 4-(4-(1-((3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl)thio)-1-methylethyl)thio-2,6-bis(1,1-dimethylethyl)phenoxy)-4-oxo-1-butyl sodium sulfate (IIa) (9.23 g).

L103 ANSWER 81 OF 198 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2001-565414 [63] WPIX

DOC. NO. CPI: C2001-167820

TITLE: Use of **mibefradil** analogs to treat and/or prevent diabetes and microvascular and macrovascular diseases..

DERWENT CLASS: B02

INVENTOR(S): HANSEN, J B; LI, M; TAGMOSE, T M

PATENT ASSIGNEE(S): (NOVO) NOVO NORDISK AS; (SALA-N) SOUTH ALABAMA MEDICAL SCI FOUND; (HANS-I) HANSEN J B; (LIMM-I) LI M; (TAGM-I) TAGMOSE T M

COUNTRY COUNT: 94

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2001062740	A1	20010830	(200163)*	EN	26	C07D235-14	--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ							
NL OA PT SD SE SL SZ TR TZ UG ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM							
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC							
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE							

SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW  
 AU 2001035363 A 20010903 (200202) C07D235-14<--  
 US 2001049447 A1 20011206 (200203) C07D235-14<--

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
WO 2001062740	A1	WO 2001-DK128	20010223	<--
AU 2001035363	A	AU 2001-35363	20010223	<--
US 2001049447	A1 Provisional	US 2000-185583P	20000228	<--
	Cont of	WO 2001-DK128	20010223	<--
		US 2001-818398	20010327	<--

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001035363	A Based on	WO 2001062740

PRIORITY APPLN. INFO: **US 2000-185583P**  
**20000228; DK 2000-293**  
**20000225**

## INT. PATENT CLASSIF.:

MAIN: C07D235-14  
 SECONDARY: A61K031-4184; A61P005-48; **A61P009-00**

## BASIC ABSTRACT:

WO 2001062740 A UPAB: 20011031

NOVELTY - **Mibefradil** analogs (I) and their salts are new.

DETAILED DESCRIPTION - Compounds of formula (I) and their salts are new:

R1, R2, R3 = H, 1-6C alkyl, 3-6C cycloalkyl, 3-6C cycloalkyl(1-6C)alkyl or 1-6C alkyl(3-6C)cycloalkyl.

ACTIVITY - Antidiabetic, cardiant, cerebroprotective, antiarteriosclerotic; ophthalmological.

MECHANISM OF ACTION - T-type and L-type **calcium channel** blocker.

USE - (I) is used to treat and/or prevent type 1 and type 2 diabetes as well as microvascular or macrovascular diseases associated with diabetes including retinopathy, nephropathy, neuropathy, gangrene, myocardial infarction, cerebral stroke and atherosclerosis.

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B06-D05; **B14-F01B; B14-F02;**  
**B14-F02D;** B14-F07; B14-L06; B14-N03;  
 B14-N10; B14-N16; B14-S04

TECH UPTX: 20011031

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) are prepared by reacting 2-(2-((3-(1-benzimidazol-2-yl)-propyl)-methyl-amino)-ethyl)-6-fluoro-1-isopropyl-1,2,3,4-tetrahydro-2-naphthalinol with an activated carboxylic acid of formula (III):

X = a leaving group e.g. halo, azide, alkoxy, phenoxy or carbonyloxy.

ABEX UPTX: 20011031

SPECIFIC COMPOUNDS - 6 compounds are specifically claimed e.g. (1S, 2S)-2-(2-(N-((3-benzimidazol-2-yl)propyl)-N-methylamino)ethyl)-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl valeroate of formula (Ia).

ADMINISTRATION - Administration may be topical including aphthalmic, vaginal, rectal, intranasal or transdermal, oral or parenteral including

intravenous drip or infusion, subcutaneous, intraperitoneal or intramuscular injection, pulmonary administration e.g. by inhalation or insufflation, intrathecal or intraventricular. Dosage none given.  
 EXAMPLE - 2-(2-((3-(1-benzimidazol-2-yl)-propyl)-methyl-amino)-ethyl)-6-fluoro-1-isopropyl-1,2,3,4-tetrahydro-2-naphthalinol (0.08 g) was dissolved in dichloromethane (2 ml). Diisopropylethylamine (0.033 ml) and valeroylchloride (0.07 ml) was added. after stirring for 70 hours, aqueous saturated sodium hydrogen carbonate was added. The aqueous layer was extracted with dichloromethane (x2). The combined organic extracts were dried (sodium sulfate) and concentrated. The residue was purified by flash chromatography using dichloromethane/methanol 6:1 as eluant to give the free base compound. This was then dissolved in ethanol and aqueous hydrochloride (1N , 0.38 ml) was added. After stirring for 30 minutes the mixture was concentrated. The residue was crystallized from ethyl acetate to give (1S, 2S)-2-(2-(N-((3-benzimidazol-2-yl)propyl)-N-methylamino)ethyl)-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl valeroate dihydrochloride.

L103 ANSWER 82 OF 198 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 2001-452570 [49] WPIX  
 DOC. NO. CPI: C2001-136845  
 TITLE: Inhibition of epithelial cell adhesion in vivo or in vitro using the **calcium channel** blocker **mibefradil**, especially useful for preventing post-cataract formation after cataract surgery.  
 DERWENT CLASS: A96 B02 D22  
 INVENTOR(S): BECK, R; GUTHOFF, R; NEBE, B; RYCHLY, J  
 PATENT ASSIGNEE(S): (BECK-I) BECK R; (GUTH-I) GUTHOFF R; (NEBE-I) NEBE B; (RYCH-I) RYCHLY J  
 COUNTRY COUNT: 1  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
DE 19954788	A1	20010531	(200149)*		6	A61K031-4184<--	

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
DE 19954788	A1	DE 1999-1054788	19991115 <--

PRIORITY APPLN. INFO: **DE 1999-19954788**  
**19991115**

INT. PATENT CLASSIF.:

MAIN: A61K031-4184

## BASIC ABSTRACT:

DE 19954788 A UPAB: 20010831

NOVELTY - The use of the **calcium channel** blocker

**mibefradil** (I) (i.e. (1S,2S)-2-(2-((3-(2-benzimidazolyl)-propyl)-methylamino)-ethyl)-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate) for inhibiting the adhesion of epithelial cells, in vivo or in vitro, is new.

ACTIVITY - Ophthalmological.

MECHANISM OF ACTION - **Calcium T-channel** blocker;  
 reduced expression of adhesion receptors; variation of the expression pattern of adhesion receptor subpopulations; increased cytoskeleton fragility; reduced adhesion receptor-cytoskeleton association; blockade of

intracellular calcium increase after stimulation by cell-specific agents or other cell-physiological processes.

In tests for the inhibition of adhesion receptor-cytoskeleton association in mHepR1 cells in vitro, (I) at 8.8 micro M reduced the mean **channel** fluorescence from **ca.** 500 (in controls) to **ca.** 460.

USE - (I) is specifically used in vitro for inhibiting cell adhesion and associated growth in various tissues (e.g. the posterior capsule wall of the eye) and/or on synthetic implants or in vitro for inhibiting cell adhesion in cell cultures, on cell culture vessels or on substrates such as biomaterials (all claimed). In particular (I) is useful for preventing the formation of post-cataracts (due to migration and proliferation of lens epithelial cells on the posterior capsule wall of the eye) after cataract surgery.

ADVANTAGE - (I) provides effective and lasting inhibition of post-cataract formation.

Dwg.0/3

FILE SEGMENT: CPI  
FIELD AVAILABILITY: AB; DCN  
MANUAL CODES: CPI: A04-F06E5; A12-V02A; B06-D05; B11-C04A;  
**B14-F02B2**; B14-L06; B14-N03; D09-A01

TECH UPTX: 20010831

TECHNOLOGY FOCUS - POLYMERS - Preferred Materials: (I) may be incorporated in synthetic lens implants of surface-modified polymethyl methacrylate.

ABEX UPTX: 20010831

ADMINISTRATION - (I) is administered in pure form or as a chemically modified derivative, in solution or carrier-bound form, typically on synthetic lens implants (e.g. of surface-modified polymethyl methacrylate) (all claimed). No effective doses or active concentrations are given.

L103 ANSWER 83 OF 198 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2000-303380 [26] WPIX

DOC. NO. CPI: C2000-091988

TITLE: Treatment of androgen-related conditions, e.g. benign prostatic hyperplasia, prostate cancer, prostatitis or hematuria, by administering a combination of 5alpha-reductase inhibitor and **calcium channel** blocker.

DERWENT CLASS: B05

INVENTOR(S): WALDSTREICHER, J; WANG, D Z

PATENT ASSIGNEE(S): (MERI) MERCK & CO INC

COUNTRY COUNT: 88

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2000018402	A1	20000406	(200026)*	EN	42	A61K031-435<--	
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL							
OA PT SD SE SL SZ TZ UG ZW							
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES							
FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT							
LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM							
TR TT TZ UA UG US UZ VN YU ZA ZW							
AU 9962638	A	20000417	(200035)			A61K031-435<--	
US 6268377	B1	20010731	(200146)			A61K031-435<--	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
-----			

WO 2000018402	A1	WO 1999-US22225	19990924	<--
AU 9962638	A	AU 1999-62638	19990924	<--
US 6268377	B1 Provisional	US 1998-102018P	19980928	<--
		US 1999-401135	19990922	<--

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
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AU 9962638	A Based on	WO 2000018402

PRIORITY APPLN. INFO: US 1998-102018P

19980928; US

1999-401135 19990922

INT. PATENT CLASSIF.:

MAIN: A61K031-435

SECONDARY: A61K031-44

BASIC ABSTRACT:

WO 200018402 A UPAB: 20000531

NOVELTY - Androgen-related condition is treated by administering a **calcium channel** blocker in combination with a 5 alpha-reductase inhibitor.

ACTIVITY - Cytostatic; antiinflammatory. For the inhibition of 5 alpha-reductase type 1, the compounds have IC50 values lower than 600 nM (the majority of compounds have IC50 values of 0.3-200 nM). For inhibition of 5 alpha-reductase type 2 the compounds have IC50 values greater than 155 nM (the majority of the compounds have IC50 values greater than 1000 nM).

MECHANISM OF ACTION - **Calcium channel** blocker, 5 alpha-reductase inhibitor.

USE - The composition is useful for treating androgen-related condition such as prostatitis, prostatic cancer, hematuria and preferably benign prostatic hyperplasia. It is also useful for preventing prostatic cancer (all claimed).

Dwg.0/4

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; DCN

MANUAL CODES: CPI: B01-C09; B06-D01; B06-D13; B06-D18; B06-F03;  
B07-D04D; B07-D11; B10-A10; B10-A15; B10-B03B;  
B10-B04B; B14-C03; B14-D05D; **B14-F02B2**;  
B14-H01B; B14-N07A

TECH UPTX: 20000531

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The 5alpha-reductase inhibitor is a compound of formula (I)-(V), or their salts or esters.

R = 1-10C alkyl (optionally substituted by 1-3 halo), phenyl or benzyl (both optionally substituted by 1-3 halo, methyl, trifluoromethyl).

The **calcium channel** blocker is a compound of formula (VI)-(X) or their salts.

R1 = 1-6C alkyl or 1-6C alkoxy-1-6C alkyl;

R2 = 1-6C alkyl, 1-6C alkoxy-1-6C alkyl, N(R4)2-1-6C alkoxy-1-6C alkyl or aryl-1-6C alkyl-N(R4)-1-6C alkyl;

R3 = H or OH;

R4 = H, methyl or ethyl;

R5 = H or heterocyclo-1-3C alkyl;

X = NO2, trifluoromethyl, 1,1-difluoromethoxy, methoxy or halo;

Y' = H or halo;

R6 = H, methoxy, OH or halo;

R7 = H, 1-5C alkyl, (un)saturated 3-6C cycloalkyl, benzyl or phenyl;

R8 = CN; or

R7 + R8 = form SO<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>SO<sub>2</sub>-;  
 R14 = phenyl or benzyl;  
 R9 = phenyl (optionally substituted with 1-3 1-8C alkyl, 1-8C alkoxy or halo);  
 R10 = H or 2-8C alkanoyl;  
 R11, R12 = 1-8C alkyl;  
 X1, R13 = H or halo; and  
 Y1 = 2-3C alkylene.

The 5 $\alpha$ -reductase inhibitor is finasteride. The **calcium channel** blocker is preferably nifedipine, nicardipine, nitrendipine, nisoldipine, felodipine, nimodipine, niludipine, amlodipine, flordipine, ryosidine, FR 7534, nilvadipine, PY 108-068, isradipine, verapamil, gallopamil, prenylamine, fendiline, terodiline, bepridil, terbutaline, amiloride, bencyclane, etafenone, diltiazem, flunarizine, cinnarizine, lidoflazine, perhexiline or **mibefradil**.

ABEX UPTX: 20000531

ADMINISTRATION - Administration is oral (claimed).

EXAMPLE - An oral composition comprised finasteride (5 mg) and nifedipine (10 mg) formulated with lactose to provide a total amount of 580-590 mg to fill a size 0 hard gelatin capsule.

L103 ANSWER 84 OF 198 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2000-147536 [13] WPIX

DOC. NO. CPI: C2000-046258

TITLE: Composition for treating e.g. hypertension and myocardial infarction comprises AT1 antagonist comprising valsartan and **calcium channel** blocker.

DERWENT CLASS: B05

INVENTOR(S): GASPARO, M; WEBB, R L; DE GASPARO, M; GASPARO, M D

PATENT ASSIGNEE(S): (NOVS) NOVARTIS AG; (NOVS) NOVARTIS-ERFINDUNGEN VERW GES MBH; (GASP-I) GASPARO M D; (WEBB-I) WEBB R L

COUNTRY COUNT: 87

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2000002543	A2	20000120	(200013)*	EN	14	A61K031-00<--	
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL							
OA PT SD SE SL SZ UG ZW							
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB							
GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU							
LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR							
TT UA UG US UZ VN YU ZA ZW							
AU 9950349	A	20000201	(200028)			A61K031-00<--	
NO 2001000113	A	20010309	(200123)			A61K000-00<--	
BR 9912021	A	20010403	(200128)			A61K031-00<--	
EP 1096932	A2	20010509	(200128)	EN		A61K031-41<--	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT							
RO SE SI							
US 6204281	B1	20010320	(200129)#		5	A61K031-41<--	
CZ 2001000087	A3	20010516	(200132)			A61K031-41<--	
SK 2001000031	A3	20010611	(200157)			A61K031-00<--	
CN 1312715	A	20010912	(200202)			A61K031-41<--	
US 2001049384	A1	20011206	(200203)#			A61K031-41<--	
KR 2001079517	A	20010822	(200213)			A61K031-41<--	
MX 2001000322	A1	20010501	(200227)			A61K031-00<--	
HU 2001002828	A2	20020429	(200238)			A61K031-41	
ZA 2001000232	A	20020529	(200240)		30	A61K000-00	
US 6395728	B2	20020528	(200243)#			A61K031-55	

JP 2002520274	W	20020709 (200259)	24 A61K031-41
AU 753486	B	20021017 (200280)	A61K031-00
NZ 509260	A	20030926 (200366)	A61K031-41
AU 2003200032	A1	20030410 (200433) #	A61K031-00
KR 2004078140	A	20040908 (200506)	A61K031-41
RU 2243768	C2	20050110 (200511)	A61K031-41
NZ 527598	A	20050429 (200532)	A61K031-275

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
WO 2000002543	A2	WO 1999-EP4842	19990709	<--
AU 9950349	A	AU 1999-50349	19990709	<--
NO 2001000113	A	WO 1999-EP4842	19990709	<--
		NO 2001-113	20010108	<--
BR 9912021	A	BR 1999-12021	19990709	<--
		WO 1999-EP4842	19990709	<--
EP 1096932	A2	EP 1999-934647	19990709	<--
		WO 1999-EP4842	19990709	<--
US 6204281	B1 Provisional	US 1998-155262P	19980710	<--
		US 1999-349654	19990708	<--
CZ 2001000087	A3	WO 1999-EP4842	19990709	<--
		CZ 2001-87	19990709	<--
SK 2001000031	A3	WO 1999-EP4842	19990709	<--
		SK 2001-31	19990709	<--
CN 1312715	A	CN 1999-809776	19990709	<--
US 2001049384	A1 Div ex	US 1999-349654	19990708	<--
		US 2001-757413	20010109	<--
KR 2001079517	A	KR 2001-700323	20010109	<--
MX 2001000322	A1	MX 2001-322	20010110	<--
HU 2001002828	A2	WO 1999-EP4842	19990709	<--
		HU 2001-2828	19990709	<--
ZA 2001000232	A	ZA 2001-232	20010109	<--
US 6395728	B2 Div ex	US 1999-349654	19990708	<--
		US 2001-757413	20010109	<--
JP 2002520274	W	WO 1999-EP4842	19990709	<--
		JP 2000-558803	19990709	<--
AU 753486	B	AU 1999-50349	19990709	<--
NZ 509260	A	NZ 1999-509260	19990709	<--
		WO 1999-EP4842	19990709	<--
AU 2003200032	A1 Div ex	AU 1999-50349	19990709	<--
		AU 2003-200032	20030107	
KR 2004078140	A	KR 2004-711566	20040727	
RU 2243768	C2	WO 1999-EP4842	19990709	<--
		RU 2001-102585	19990709	<--
NZ 527598	A Div ex	NZ 1999-509260	19990709	<--
		NZ 1999-527598	19990709	<--

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9950349	A Based on	WO 2000002543
BR 9912021	A Based on	WO 2000002543
EP 1096932	A2 Based on	WO 2000002543
CZ 2001000087	A3 Based on	WO 2000002543
SK 2001000031	A3 Based on	WO 2000002543
US 2001049384	A1 Div ex	US 6204281
HU 2001002828	A2 Based on	WO 2000002543

US 6395728	B2 Div ex	US 6204281
JP 2002520274	W Based on	WO 2000002543
AU 753486	B Previous Publ.	AU 9950349
	Based on	WO 2000002543
NZ 509260	A Div in	NZ 527598
	Based on	WO 2000002543
RU 2243768	C2 Based on	WO 2000002543
NZ 527598	A Div ex	NZ 509260

PRIORITY APPLN. INFO: **US 1998-113893**  
**19980710; US**  
**1999-349654**      **19990708;**  
**US 2001-757413**  
**20010109; AU 2003-200032**  
**20030107**

## INT. PATENT CLASSIF.:

MAIN: A61K000-00; A61K031-00; A61K031-275; A61K031-41;  
A61K031-55

SECONDARY: A01N043-64; A61K031-135; A61K031-137; A61K031-277;  
A61K031-4184; A61K031-44; A61K031-4422; A61K031-4439;  
A61K031-495; A61K031-554; A61K045-06; A61P003-10;  
A61P005-48; **A61P009-00; A61P009-04;**  
**A61P009-06; A61P009-10;**  
**A61P009-12; A61P011-00; A61P013-12; A61P015-12;**  
A61P025-06; A61P025-28; A61P027-02; A61P039-00;  
A61P043-00

INDEX: A61K031-41; A61K031:277; A61K031:44; A61K031:55

## BASIC ABSTRACT:

WO 200002543 A UPAB: 20010620

NOVELTY - Composition comprises AT1-antagonist comprising valsartan or its salts and a **calcium channel** blocker or its salts.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for a combination composition comprising (i) the AT1-antagonist valsartan or a salt and (ii) a **calcium channel** blocker or salt

ACTIVITY - Antihypertensive; antiarrhythmic; antianginal; cardiant; antiarteriosclerotic; antidiabetic; analgesic; neuroprotective; CNS.

Diabetes was induced in spontaneously hypertensive rats which were then monitored for 21 weeks. Survival in a group treated with 20 mg/kg valsartan and 15 mg/kg verapamil was 67.1% compared to 42.9% in a group treated with 20 mg/kg verapamil, 45.9% in a group treated with 30 mg/kg valsartan and 29.7% in a control group.

MECHANISM OF ACTION - AT1-antagonist; **calcium channel** blocker.

USE - Used for treating hypertension, (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, myocardial infarction and its sequelae, supraventricular and ventricular arrhythmias, atrial fibrillation or atrial flutter, atherosclerosis, angina (whether stable or unstable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, hypertension in diabetic patients, hypertension in patients with NIDDM, secondary aldosteronism, primary and secondary pulmonary hyperaldosteronism, primary and pulmonary hypertension, renal failure conditions, diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, migraine, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, Alzheimer's disease and stroke.

Dwg.0/0

FILE SEGMENT: CPI  
FIELD AVAILABILITY: AB; DCN



MANUAL CODES: CPI: B06-D05; B06-F03; B07-B03; B07-D04B; B07-D13;  
 B10-A15; B10-B04B; B14-C01; **B14-F01A;**  
**B14-F01B; B14-F01D;**  
**B14-F02B; B14-F02B2;** B14-F07;  
 B14-J01A4; B14-L06; B14-N03; B14-N07; B14-N10;  
 B14-N16; B14-S01; B14-S04

TECH UPTX: 20000313

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Drugs: The **calcium channel** blocker comprises amlodipine, felodipine, ryosidine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, nivaldipine, flunarizine, prenylamine, diltiazem, fendiline, gallopamil, **mibefradil**, anipamil, tiapamil or verapamil.

ABEX UPTX: 20000313

ADMINISTRATION - The oral dosage is 10-200 mg valsartan and 1-180 mg **calcium channel** blocker.

L103 ANSWER 85 OF 198 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2000-147527 [13] WPIX

DOC. NO. CPI: C2000-046253

TITLE: Hypericin, its derivatives and analogs, and Hypericum extracts as specific T-type **calcium channel** blockers, useful in treatment of cardiovascular, central nervous system, and endocrine disorders.

DERWENT CLASS: B05

INVENTOR(S): LING, L; PANG, P K T; SHAN, J J; WU, X

PATENT ASSIGNEE(S): (CVTE-N) CV TECHNOLOGIES INC

COUNTRY COUNT: 87

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2000002455	A1	20000120	(200013)*	EN	32	A01N065-00<--	
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL							
OA PT SD SE SL SZ UG ZW							
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB							
GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU							
LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR							
TT UA UG US UZ VN YU ZA ZW							
AU 9949581	A	20000201	(200028)			A01N065-00<--	
EP 1094712	A1	20010502	(200125)	EN		A01N065-00<--	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT							
RO SE SI							
CN 1308492	A	20010815	(200174)			A01N065-00<--	
KR 2001071822	A	20010731	(200208)			A61K035-78<--	
JP 2002520260	W	20020709	(200259)		40	A61K031-12	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000002455	A1	WO 1999-US14132	19990709 <--
AU 9949581	A	AU 1999-49581	19990709 <--
EP 1094712	A1	EP 1999-933542	19990709 <--
		WO 1999-US14132	19990709 <--
CN 1308492	A	CN 1999-808429	19990709 <--
KR 2001071822	A	KR 2001-700390	20010109 <--
JP 2002520260	W	WO 1999-US14132	19990709 <--
		JP 2000-558725	19990709 <--

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9949581	A Based on	WO 2000002455
EP 1094712	A1 Based on	WO 2000002455
JP 2002520260	W Based on	WO 2000002455

PRIORITY APPLN. INFO: **US 1998-92227P**  
**19980709**

## INT. PATENT CLASSIF.:

MAIN: A01N065-00; A61K031-12; A61K035-78  
 SECONDARY: A01N029-00; A01N035-00; A61K031-19; A61K031-215;  
 A61P003-08; A61P003-10; A61P007-00; **A61P009-00**;  
**A61P009-04**; **A61P009-06**;  
**A61P009-12**; A61P025-06; A61P025-08; A61P025-24;  
 A61P025-28; A61P043-00; C07C017-00; C07C019-08;  
 C07C022-00; C07C049-657; C07C049-687; C07C049-703;  
 C07C065-36; C07C069-007; C07C069-017; C07C069-95;  
 C07C309-44; C07C309-57

## BASIC ABSTRACT:

WO 200002455 A UPAB: 20000313

NOVELTY - Method of treating disorders, other than depression or migraine headache, mediated by a T-type **calcium channel** blocker, by administration of Hypericum perforatum, an extract or constituent of a species of Hypericum genus, or a hypericin derivative or analog is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for hypericin derivatives of formula (I).

R1, R6, R7, R12 = H, hydroxy, OR, or OCOR;

R2, R5, R8, R11 = H, R, halogen, or SO<sub>3</sub>H;

R3, R4, R9, R10 = H, R hydroxy, OR, OCOR, CH<sub>2</sub>OH, CH<sub>2</sub>OR, CH<sub>2</sub>OCOR, COOH, or COOR; and

R = 1-30C alkyl (optionally substituted); provided that the following compounds, all having

R2, R5, R8, R11 = H, are excluded; and

(a) R1, R3, R4, R6, R7, R12 = hydroxy;

R9, R10 = methyl;

(b) R1, R6, R7, R9, R10, R12 = hydroxy;

R3, R4 = methyl;

(c) R1, R3, R4, R6, R7, R12 = hydroxy;

R9 = methyl;

R10 = CH<sub>2</sub>OH;

(d) R1, R3, R4, R6, R7, R12 = hydroxy;

R9 = CH<sub>2</sub>OH, and R10 = methyl;

(e) R1, R6, R7, R9, R10, R12 = hydroxy;

R3 = methyl;

R4 = CH<sub>2</sub>OH;

(f) R1, R6, R7, R9, R10, R12 = hydroxy;

R3 = CH<sub>2</sub>OH, and R4 = methyl.

ACTIVITY - Cardiovascular; Nootropic; Neuroprotective.

MECHANISM OF ACTION - The Hypericum extracts, hypericin, and other materials mentioned are selective T-type **calcium channel** blockers, as opposed to non-selective L-type blockers. This could lead to a higher therapeutic index and safety over the conventional L-type blockers and has already been found with **mibefradil**, a selective T-type blocker. **Mibefradil** induces peripheral and coronary vasodilation without symathetic activation or inotropic effects, increases coronary blood flow without increasing oxygen consumption, and causes

slight heart rate reduction, inducing diastolic relaxation and improving subendocardial and small artery perfusion. T-type blockers also facilitate insulin secretion and steroidogenesis.

Mouse neuroblastoma cells were cultured to express either T- or L-type **calcium channel** currents. The results showed that hypericin affects T-type channel currents in a dose dependent manner. It was also demonstrated that hypericin does not affect the L-type calcium current at up to 10  $\mu$ M; and that nifedipine, a well known **calcium channel** blocker, inhibited the L-type currents at 1  $\mu$ M to 40% of the controls.

USE - The Hypericin extracts, hypericin, and other materials mentioned are of value in the treatment of chronic or congestive heart failure, ischemia, arrhythmia, angina, hypertension, hypo- and hyper-insulinemia, diabetes, hyperaldosteronemia, epilepsy, brain aging or other neurodegenerative diseases (e.g., Alzheimer's disease), and pre-term labor; and with the inclusion of depression and migraine headache when not excluded by the provisos. The therapeutic agents are optionally given in combination, and therefore synergistic effects (not clearly specified) may occur.

Dwg.0/7

FILE SEGMENT: CPI  
 FIELD AVAILABILITY: AB; GI; DCN  
 MANUAL CODES: CPI: B04-A08; B04-A10; B06-D05; B08-A; B09-A; B10-E04A;  
 B14-C01; **B14-F01**; **B14-F01A**;  
**B14-F01D**; **B14-F01E**; B14-F09;  
 B14-F10; B14-J01A; B14-J01A1; B14-J01A3; B14-J01A4;  
 B14-J01B; B14-J07; B14-P03; B14-S04; B14-S09

ABEX UPTX: 20000313

SPECIFIC COMPOUNDS - Hypericin analogs include pseudohypericin and hyperforin.

ADMINISTRATION - Includes oral, parenteral, topical, rectal, or ophthalmological. Amounts, for Hypericum extracts are 0.05-500 (preferably 0.5-50) mg/kg/day; for hypericin and its derivatives and analogs, 0.0001-10 (preferably 0.0015-0.15) mg/kg/day for hypericin and 0.001-5 mg/kg/day for derivatives and analogs.

=> d ibib ed ab hitind 86-

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, TOXCENTER, MEDLINE, BIOSIS, PASCAL, DRUGU, SCISEARCH, EMBASE, WPIX' - CONTINUE? (Y)/N:y

YOU HAVE REQUESTED DATA FROM 113 ANSWERS - CONTINUE? Y/(N):  
 YOU HAVE REQUESTED DATA FROM 113 ANSWERS - CONTINUE? Y/(N):y

L103 ANSWER 86 OF 198 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS  
 RESERVED. on STN DUPLICATE 24

ACCESSION NUMBER: 1998039498 EMBASE  
 TITLE: T-type  $\text{Ca}^{2+}$  channels and pharmacological blockade:  
 Potential pathophysiological relevance.  
 AUTHOR: Ertel S.I.; Ertel E.A.; Clozel J.-P.  
 CORPORATE SOURCE: Dr. J.-P. Clozel, Pharma Division, Preclinical Research, F.  
 Hoffmann-La Roche Ltd, CH-4070 Basel, Switzerland  
 SOURCE: Cardiovascular Drugs and Therapy, (1997) Vol. 11, No. 6,  
 pp. 723-739.  
 Refs: 216  
 ISSN: 0920-3206 CODEN: CDTHET  
 COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery  
029 Clinical Biochemistry  
030 Pharmacology  
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 19980220

Last Updated on STN: 19980220

ED Entered STN: 19980220

Last Updated on STN: 19980220

AB Low-voltage-activated T-type  $\text{Ca}^{2+}$  channels are present in most excitable tissues including the heart (mainly pacemaker cells), smooth muscle, central and peripheral nervous systems, and endocrine tissues, but also in non-excitabile cells, such as osteoblasts, fibroblasts, glial cells, etc. Although they comprise a slightly heterogeneous population, these channels share many defining characteristics: small conductance ( $< 10 \text{ pS}$ ), similar  $\text{Ca}^{2+}$  and  $\text{Ba}^{2+}$  permeabilities, slow deactivation, and a voltage-dependent inactivation rate. In addition, activation at low voltages, rapid inactivation, and blockade by  $\text{Ni}^{2+}$  are classical properties of T-type  $\text{Ca}^{2+}$  channels, which are less specific. T-type  $\text{Ca}^{2+}$  channels are weakly blocked by standard  $\text{Ca}^{2+}$  antagonists. Pharmacological blockers are scarce and often lack specificity and/or potency. The physiological modulation of T-type  $\text{Ca}^{2+}$  currents is complex: they are enhanced by endothelin-1, angiotensin II (AT1-receptor), ATP, and isoproterenol (cAMP-independent), but are reduced by angiotensin II (AT2-receptor), somatostatin and atrial natriuretic peptide. Norepinephrine enhances these currents in some cells but decreases them in others. T-type  $\text{Ca}^{2+}$  currents have many known or suggested physiological and pathophysiological roles in growth (protein synthesis, cell differentiation, and proliferation), neuronal firing regulation, some aspects of genetic hypertension, cardiac hypertrophy, cardiac fibrosis, cardiac rhythm (normal and abnormal), and atherosclerosis. **Mibefradil** is a new  $\text{Ca}^{2+}$  antagonist that is effective in hypertension and angina pectoris. Its favorable pharmacological profile and limited side effects appear to be related to selective block of T-type  $\text{Ca}^{2+}$  channels: **mibefradil** reduces vascular resistance and heart rate without negative inotropy or neurohormonal stimulation, and it also has significant antiproliferative actions.

CT Medical Descriptors:

**\*calcium channel**

pathophysiology

**calcium conductance**

**calcium current**

protein synthesis

cell differentiation

cell proliferation

action potential

**hypertension: DT, drug therapy**

heart hypertrophy

heart muscle fibrosis

heart arrhythmia

atherosclerosis

**angina pectoris: DT, drug therapy**

heart rate

vascular resistance

**heart**

smooth muscle

peripheral nervous system

central nervous system

osteoblast

fibroblast  
glia cell  
endocrine system  
electrophysiology  
channel gating  
drug structure  
human  
nonhuman  
article  
priority journal  
Drug Descriptors:

\*calcium channel blocking agent: PD, pharmacology

\*calcium ion: EC, endogenous compound

barium ion  
nickel  
endothelin 1  
angiotensin  
adenosine triphosphate  
isoprenaline  
somatostatin  
atrial natriuretic factor  
noradrenalin

mibefradil: DT, drug therapy

mibefradil: PD, pharmacology

dihydropyridine derivative: PD, pharmacology

felodipine: PD, pharmacology

isradipine: PD, pharmacology

tetramethrin: PD, pharmacology

octanol: PD, pharmacology

tetrandrine: PD, pharmacology

diphenylbutylpiperidine derivative: PD, pharmacology

penfluridol: PD, pharmacology

fluspirilene: PD, pharmacology

amiodarone: PD, pharmacology

bepiridil: PD, pharmacology

cinnarizine: PD, pharmacology

flunarizine: PD, pharmacology

RN (calcium ion) 14127-61-8; (barium ion) 22541-12-4; (nickel) 7440-02-0;  
(angiotensin) 11128-99-7, 1407-47-2; (adenosine triphosphate) 15237-44-2,  
56-65-5, 987-65-5; (isoprenaline) 299-95-6, 51-30-9, 6700-39-6, 7683-59-2;  
(somatostatin) 38916-34-6, 51110-01-1; (atrial natriuretic factor)  
85637-73-6; (noradrenalin) 1407-84-7, 51-41-2; (mibefradil)  
116666-63-8; (felodipine) 72509-76-3; (isradipine) 75695-93-1;  
88977-22-4; (tetramethrin) 7696-12-0; (octanol) 111-87-5, 29063-28-3;  
(tetrandrine) 518-34-3; (penfluridol) 26864-56-2; (fluspirilene)  
1841-19-6; (amiodarone) 1951-25-3, 19774-82-4, 62067-87-2; (bepiridil)  
64706-54-3, 68099-86-5; (cinnarizine) 298-57-7; (flunarizine) 30484-77-6,  
52468-60-7

L103 ANSWER 87 OF 198 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS  
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ACCESSION NUMBER: 1998254535 EMBASE

TITLE: Effect of calcium channel blockers on  
noradrenaline release in the cardiovascular system.

AUTHOR: Molderings G.I.; Gothert M.

CORPORATE SOURCE: G.I. Molderings, Institute of Pharmacology/Toxicology,  
University of Bonn, Reuterstr. 2b, D-53113 Bonn, Germany

SOURCE: Pharmacology and Toxicology, Supplement, (1998) Vol. 83,  
No. 1, pp. 84-86.

ISSN: 0901-9936 CODEN: PTSUEC

COUNTRY: Denmark  
DOCUMENT TYPE: Journal; Conference Article  
FILE SEGMENT: 030 Pharmacology  
037 Drug Literature Index  
LANGUAGE: English  
ENTRY DATE: Entered STN: 19980910  
Last Updated on STN: 19980910

ED Entered STN: 19980910  
Last Updated on STN: 19980910

CT Medical Descriptors:  
\*cardiovascular system  
\*calcium channel  
noradrenalin release  
amino terminal sequence  
calcium mobilization  
stimulus secretion coupling  
channel gating  
sympathetic nerve  
drug mechanism  
bradycardia  
human  
nonhuman  
mouse  
rat  
human tissue  
animal tissue  
conference paper  
priority journal  
Drug Descriptors:  
\*calcium channel blocking agent  
\*noradrenalin  
mibefradil  
dihydropyridine derivative  
nifedipine  
diltiazem  
verapamil  
omega conotoxin gvia  
omega agatoxin iva  
RN (noradrenalin) 1407-84-7, 51-41-2; (mibefradil)  
116666-63-8; (nifedipine) 21829-25-4; (diltiazem) 33286-22-5,  
42399-41-7; (verapamil) 152-11-4, 52-53-9; (omega conotoxin gvia)  
107407-86-3  
CO Hoffmann la roche (Germany)

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RESERVED. on STN

ACCESSION NUMBER: 1998168868 EMBASE  
TITLE: The physiological and pharmacological significance of  
cardiovascular T- type, voltage-gated calcium  
channels.  
AUTHOR: Triggle D.J.  
CORPORATE SOURCE: Dr. D.J. Triggle, Graduate School-SUNY, 415 Capen Hall,  
Buffalo, NY 14260, United States  
SOURCE: American Journal of Hypertension, (1998) Vol. 11, No. 4 III  
SUPPL., pp. 80S-87S.  
Refs: 44  
ISSN: 0895-7061 CODEN: AJHYE6  
PUBLISHER IDENT.: S 0895-7061(98)00004-1  
COUNTRY: United States  
DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery  
037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 19980727  
Last Updated on STN: 19980727

ED Entered STN: 19980727

Last Updated on STN: 19980727

AB An influx of calcium ions into cells, made possible by the opening of specific, voltage-gated channels, triggers muscular contraction and several other physiological processes. Two types of **calcium channels**, L-type and T-type, are found in the cardiovascular system. These two types of channels differ considerably in their electrical and chemical characteristics and in their distribution in tissue. The L-type **calcium channel** is responsible for normal myocardial contractility and for vascular smooth muscle contractility. In contrast, T-type **calcium channels** are not normally present in the adult myocardium, but are prominent in conducting and pacemaking cells. They are thought to help regulate vascular tone, signal conduction, cardiac pacemaking, and the secretion of certain intercellular transmitters. T-Type channels also seem to have an important role in normal growth processes and in the tissue remodeling that occurs in pathologic processes such as cardiac hypertrophy. Traditional calcium antagonists act on L-type channels. **Mibefradil** is a recently characterized calcium antagonist and the first that is selective for T-type **calcium channels**. This unique property may lead to major applications in cardiovascular medicine.

CT Medical Descriptors:

\***hypertension: DT, drug therapy**  
drug effect

**cardiovascular response**  
**calcium channel**

heart muscle contractility

vascular smooth muscle

blood vessel tone

heart hypertrophy

**signal transduction**

cell compartmentalization

**calcium transport**

human

review

priority journal

Drug Descriptors:

\***calcium channel blocking agent: DO, drug dose**

\***calcium channel blocking agent: DT, drug therapy**

\***calcium channel blocking agent: PD, pharmacology**

verapamil: DO, drug dose

verapamil: DT, drug therapy

verapamil: PD, pharmacology

nifedipine: DO, drug dose

nifedipine: DT, drug therapy

nifedipine: PD, pharmacology

diltiazem: DO, drug dose

diltiazem: DT, drug therapy

diltiazem: PD, pharmacology

indolizine derivative: DO, drug dose

indolizine derivative: DT, drug therapy

indolizine derivative: PD, pharmacology

**mibefradil: DO, drug dose**

mibefradil: DT, drug therapy

mibefradil: PD, pharmacology

sr 33357

RN (verapamil) 152-11-4, 52-53-9; (nifedipine) 21829-25-4; (diltiazem)  
33286-22-5, 42399-41-7; (mibefradil) 116666-63-8

CN Sr 33357

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ACCESSION NUMBER: 1998318340 EMBASE

TITLE: [Mibefradil - A calcium antagonist].

MIbefRADIL, EIN CALCIUMANTAGONIST.

AUTHOR: Peruche B.; Schulz M.

CORPORATE SOURCE: B. Peruche, Arzneimittelinformationsstelle, ABDA,  
Carl-Mannich-Strasse 26, 65760 Eschborn, Germany

SOURCE: Pharmazeutische Zeitung, (17 Sep 1998) Vol. 143, No. 38,  
pp. 44-52.

ISSN: 0031-7136 CODEN: PZSED5

COUNTRY: Germany

DOCUMENT TYPE: Journal; (Short Survey)

FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery

030 Pharmacology

037 Drug Literature Index

038 Adverse Reactions Titles

LANGUAGE: German

SUMMARY LANGUAGE: German

ENTRY DATE: Entered STN: 19981009

Last Updated on STN: 19981009

ED Entered STN: 19981009

Last Updated on STN: 19981009

CT Medical Descriptors:

\*channel gating

\*calcium channel

\*angina pectoris: DT, drug therapy

\*hypertension: DT, drug therapy

calcium transport

smooth muscle

leg edema: SI, side effect

fatigue: SI, side effect

vertigo: SI, side effect

atrioventricular block: SI, side effect

sinus bradycardia: SI, side effect

human

short survey

Drug Descriptors:

\*mibefradil: AE, adverse drug reaction

\*mibefradil: AN, drug analysis

\*mibefradil: CB, drug combination

\*mibefradil: CM, drug comparison

\*mibefradil: DV, drug development

\*mibefradil: IT, drug interaction

\*mibefradil: DT, drug therapy

\*mibefradil: PD, pharmacology

\*calcium antagonist: AE, adverse drug reaction

\*calcium antagonist: AN, drug analysis

\*calcium antagonist: CB, drug combination

\*calcium antagonist: CM, drug comparison

\*calcium antagonist: DV, drug development

\*calcium antagonist: IT, drug interaction

\*calcium antagonist: DT, drug therapy



**\*calcium antagonist: PD, pharmacology**

placebo: CM, drug comparison

cerate

desipramine: CB, drug combination

desipramine: IT, drug interaction

antiarrhythmic agent: CB, drug combination

antiarrhythmic agent: IT, drug interaction

imipramine: CB, drug combination

imipramine: IT, drug interaction

hydroxymethylglutaryl coenzyme a reductase inhibitor: CB, drug combination

hydroxymethylglutaryl coenzyme a reductase inhibitor: IT, drug interaction

tsukubaenolide: CB, drug combination

tsukubaenolide: IT, drug interaction

simvastatin: CB, drug combination

simvastatin: IT, drug interaction

mevinolin: CB, drug combination

mevinolin: IT, drug interaction

cyclosporin a: CB, drug combination

cyclosporin a: IT, drug interaction

thioridazine: CB, drug combination

thioridazine: IT, drug interaction

digoxin: CB, drug combination

digoxin: IT, drug interaction

cytochrome p450: EC, endogenous compound

unclassified drug

RN (mibefradil) 116666-63-8; (desipramine) 50-47-5,  
 58-28-6; (imipramine) 113-52-0, 50-49-7; (tsukubaenolide) 104987-11-3;  
 (simvastatin) 79902-63-9; (mevinolin) 75330-75-5; (cyclosporin a)  
 59865-13-3, 63798-73-2; (thioridazine) 130-61-0, 50-52-2; (digoxin)  
 20830-75-5, 57285-89-9; (cytochrome p450) 9035-51-2

CN (1) Posicor; (2) Cerate

CO (1) Hoffmann la roche (United Kingdom); (2) Asta (Germany)

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ACCESSION NUMBER: 1998023569 EMBASE

TITLE: Cardiovascular T-type **calcium channels**:  
 Physiological and pharmacological significance.

AUTHOR: Triggle D.J.

CORPORATE SOURCE: Dr. D.J. Triggle, The Graduate School, State University of  
 New York, 415 Capen Hall, Buffalo, NY 14260-1200, United  
 States

SOURCE: Journal of Hypertension, Supplement, (1997) Vol. 15, No. 5,  
 pp. S9-S15.  
 Refs: 59

ISSN: 0952-1178 CODEN: JHSUEW

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Conference Article

FILE SEGMENT: 002 Physiology  
 018 Cardiovascular Diseases and Cardiovascular Surgery  
 037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 19980202

Last Updated on STN: 19980202

ED Entered STN: 19980202

Last Updated on STN: 19980202

AB Cellular calcium regulation. A variety of Ca<sup>2+</sup> control processes are  
 responsible for Ca<sup>2+</sup> homeostasis and signaling. Voltage-gated Ca<sup>2+</sup>  
 channels are dominant in the cardiovascular system. Voltage-gated Ca<sup>2+</sup>

channels. There are several distinct subclasses of Ca<sup>2+</sup> channels, distinguished by location, biophysical, structural and pharmacological characteristics. They include both high- and low-voltage-activated channels. The long-lasting (L) type of high-voltage-activated channel is well characterized and is the site of action for the existing clinically available Ca<sup>2+</sup> channel antagonists: nifedipine, verapamil and diltiazem. T-type Ca<sup>2+</sup> channels. The low-voltage-activated transient (T-type) channel is widespread in the cardiovascular system and in neurons. It serves pacemaking functions and supports Ca<sup>2+</sup> signaling in secretory cells and vascular smooth muscle. The T-type channel also functions in cell growth processes under physiological and pathological conditions. **Mibefradil** as a T-type Ca<sup>2+</sup> channel antagonist.

**Mibefradil** (Ro 40-5967) is a structurally novel Ca<sup>2+</sup> antagonist with selectivity for T-type over L-type channels. This selectivity may underlie its vasodilating activity and heart rate depressive effect, its lack of negative inotropy and its cardioprotective properties.

CT Medical Descriptors:

- \*calcium channel
- \*cardiovascular system

physiology

pharmacology

- calcium homeostasis

- signal transduction

pacemaker

heart electrophysiology

vasodilatation

heart rate

heart protection

human

conference paper

priority journal

Drug Descriptors:

- calcium antagonist

- mibefradil

nifedipine

verapamil

diltiazem

RN (mibefradil) 116666-63-8; (nifedipine) 21829-25-4;

(verapamil) 152-11-4, 52-53-9; (diltiazem) 33286-22-5, 42399-41-7

CN Ro 40 5967

L103 ANSWER 91 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN DUPLICATE 12

ACCESSION NUMBER: 2000:71525 TOXCENTER

COPYRIGHT: Copyright (c) 2005 The Thomson Corporation

DOCUMENT NUMBER: PREV200000059276

TITLE: Case report: Rhabdomyolysis induced by mibefradil in a patient treated with cyclosporine and simvastatin

AUTHOR(S): Wombolt, Duane G.; Jackson, Angela; Pun, Rajesh; Smith, Stanley; McCune, Thomas R. [Reprint author]; Williams, Patricia B.

CORPORATE SOURCE: 907 Medical Tower, Norfolk, VA, USA

SOURCE: Journal of Clinical Pharmacology, (March, 1999)

Vol. 39, No. 3, pp. 310-312. print.

CODEN: JCPCBR. ISSN: 0091-2700.

DOCUMENT TYPE: Article

FILE SEGMENT: BIOSIS

OTHER SOURCE: BIOSIS 2000:59276

LANGUAGE: English

ENTRY DATE: Entered STN: 20011116

Last Updated on STN: 20020108

ED Entered STN: 20011116  
Last Updated on STN: 20020108  
CC Toxicology - General and methods 22501  
Anatomy and Histology - Regeneration and transplantation 11107  
Cardiovascular system - General and methods 14501  
Urinary system - General and methods 15501  
Muscle - General and methods 17501  
Pharmacology - General 22002  
CT Hypertension  
Kidney Failure  
ST Major Concepts  
Pharmacology; Toxicology  
ST Diseases  
hypertension: vascular disease  
Hypertension (MeSH)  
ST Diseases  
renal failure: urologic disease  
Kidney Failure (MeSH)  
ST Chemicals & Biochemicals  
cyclosporine: immunosuppressant-drug, combination therapy; mibefradil  
[Posicor]: antihypertensive-drug, calcium channel blocker-drug;  
simvastatin: HMG CoA reductase inhibitor-drug  
ST Methods & Equipment  
diagnosis: diagnostic method; renal transplantation: surgical method,  
therapeutic method, transplantation method  
ST Miscellaneous Descriptors  
adverse effects; drug interactions; rhabdomyolysis; Case Study  
ORGN Classifier  
Hominidae 86215  
Super Taxa  
Primates; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
human: male, middle age, patient, white  
Taxa Notes  
Animals, Chordates, Humans, Mammals, Primates, Vertebrates  
RN 59865-13-3Q (cyclosporine)  
63798-73-2Q (cyclosporine)  
116644-53-2 (mibefradil)  
116644-53-2 (Posicor)  
79902-63-9 (simvastatin)  
116666-63-8 (POSICOR)

L103 ANSWER 92 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN DUPLICATE 13  
ACCESSION NUMBER: 1998:44477 TOXCENTER  
DOCUMENT NUMBER: PubMed ID: 9640486  
TITLE: Mibefradil: a new class of **calcium-**  
**channel** antagonists  
COMMENT: Comment in: Ann Pharmacother. 1998 Dec;32(12):1372. PubMed  
ID: 9876826  
AUTHOR(S): Billups S J; Carter B L  
CORPORATE SOURCE: Kaiser Permanente, School of Pharmacy Practice, University  
of Colorado Health Sciences Center, Denver, USA  
SOURCE: Annals of pharmacotherapy, (1998 Jun) 32 (6) 659-71. Ref:  
49.  
Journal Code: 9203131. ISSN: 1060-0280.  
COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
**General Review; (REVIEW)**  
(REVIEW, TUTORIAL)

FILE SEGMENT: MEDLINE  
OTHER SOURCE: MEDLINE 1998304668  
LANGUAGE: English  
ENTRY DATE: Entered STN: 20011116  
Last Updated on STN: 20011116

ED Entered STN: 20011116

Last Updated on STN: 20011116

AB OBJECTIVE: To describe the pharmacology, pharmacokinetics, and clinical efficacy of mibefradil compared with other agents used for **hypertension** and **angina**. DATA SOURCES: A MEDLINE search was performed for the period of January 1980 through September 1997 using the key terms mibefradil or Ro 40-5967. All articles written in English were considered for review. STUDY SELECTION AND DATA EXTRACTION: All clinical studies involving mibefradil were evaluated. Preclinical data were included if these data were not adequately represented in clinical (human) studies. DATA SYNTHESIS: Mibefradil is the first member of a new class of **calcium-channel** antagonists (CCAs) that block the T-type **calcium channels**. A long elimination half-life makes once-daily dosing feasible, and the drug's lack of negative inotropy and reflex tachycardia distinguishes it from other available CCAs. When administered at recommended dosages (50 or 100 mg once daily), mibefradil reduces blood pressure over 24 hours in patients with **hypertension**, improves exercise capacity, and relieves **anginal** symptoms in patients with chronic stable **angina** pectoris. CONCLUSIONS: Clinical studies have found that the **antihypertensive** effects of mibefradil are comparable with those of nifedipine, verapamil, and amlodipine, and more effective than those of diltiazem. These effects result from peripheral vasodilation and a slight reduction in **heart** rate. Selective vasodilation of the coronary vasculature makes it an effective **antianginal** agent when used alone or added to beta-blocker therapy. Mibefradil demonstrates no significant effects on **cardiac** contractility, and no adrenergic stimulation resulting in reflex tachycardia. Therefore, it may have some advantages over currently available CCAs, especially in patients with congestive **heart** failure, although such advantages are unproven in published clinical trials. Ongoing clinical studies, including the Mortality Assessment in Congestive **Heart** Failure Trial (MACH-1) currently in progress, are needed to clarify mibefradil's place in **cardiovascular** therapy.

CT Check Tags: Female; Male

Aged

\***Angina** Pectoris: DT, drug therapy

Benzimidazoles: AE, adverse effects

Benzimidazoles: PK, pharmacokinetics

\*Benzimidazoles: PD, pharmacology

Benzimidazoles: TU, therapeutic use

**Calcium Channel** Blockers: AE, adverse effects

**Calcium Channel** Blockers: PK, pharmacokinetics

\***Calcium Channel** Blockers: PD, pharmacology

**Calcium Channel** Blockers: TU, therapeutic use

Clinical Trials

Drug Interactions

Drug Therapy, Combination

Humans

\***Hypertension**: DT, drug therapy

Mibefradil

Tetrahydronaphthalenes: AE, adverse effects

Tetrahydronaphthalenes: PK, pharmacokinetics

\*Tetrahydronaphthalenes: PD, pharmacology

Tetrahydronaphthalenes: TU, therapeutic use

RN 116644-53-2 (Mibefradil)  
CN 0 (Benzimidazoles); 0 (Calcium Channel Blockers); 0  
(Tetrahydronaphthalenes)

L103 ANSWER 93 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN DUPLICATE 14  
ACCESSION NUMBER: 1998:41027 TOXCENTER  
DOCUMENT NUMBER: PubMed ID: 9620098  
TITLE: Mibefradil, a pharmacologically distinct calcium  
antagonist  
AUTHOR(S): Ernst M E; Kelly M W  
CORPORATE SOURCE: Division of Clinical and Administrative Pharmacy, College  
of Pharmacy, University of Iowa, Iowa City 52242, USA  
SOURCE: Pharmacotherapy, (1998 May-Jun) 18 (3) 463-85. Ref: 100.  
Journal Code: 8111305. ISSN: 0277-0008.  
COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
FILE SEGMENT: MEDLINE  
OTHER SOURCE: MEDLINE 1998281408  
LANGUAGE: English  
ENTRY DATE: Entered STN: 20011116  
Last Updated on STN: 20011116

ED Entered STN: 20011116

Last Updated on STN: 20011116

AB Mibefradil is the prototype of a new class of calcium antagonists that selectively block T-type voltage-gated plasma membrane **calcium channels** in vascular smooth muscle. The drug is structurally and pharmacologically different from traditional calcium antagonists. It does not have negative inotropism at therapeutic concentrations, and is not associated with reflex activation of neurohormonal and sympathetic systems. In clinical studies of **hypertension**, mibefradil 50 and 100 mg/day reduced trough sitting diastolic and systolic blood pressures in a dose-related manner. Dosages exceeding 100 mg/day generally did not result in significantly greater efficacy, but were associated with a higher frequency of adverse events. No first-dose hypotensive phenomenon was observed. Mibefradil has **antiischemic** properties resulting from dilation of coronary and peripheral vascular smooth muscle, and a slight reduction in **heart** rate. In clinical studies of chronic stable **angina** pectoris, dose-related increases in exercise duration, time to onset of **angina**, and time to 1-mm ST-segment depression during exercise tolerance tests occurred. Mibefradil reduced the number and duration of **ischemic** events recorded by 48-hour ambulatory **electrocardiograph** (ECG) monitoring, as well as number of **anginal** episodes and nitroglycerin consumption. Favorable hemodynamic and clinical profiles are reported, including high trough:peak ratios (> 80%), high oral bioavailability, and long elimination half-life (17-25 hrs) permitting once/day dosing. Dizziness, headache, leg edema, and lightheadedness are frequently reported, but overall the agent is well tolerated. First-degree atrioventricular block and sinus bradycardia are the most frequent ECG changes caused by the drug. In vitro studies indicate mibefradil inhibits cytochrome P450 1A2, 2D6, and 3A4, resulting in elevated plasma concentrations of drugs metabolized by those isoenzymes. Therefore, it is contraindicated in patients receiving terfenadine, astemizole, cisapride, lovastatin, or simvastatin.

CT **Angina** Pectoris: DT, drug therapy

Animals

Benzimidazoles: AD, administration & dosage

Benzimidazoles: AE, adverse effects

Benzimidazoles: PK, pharmacokinetics  
 \*Benzimidazoles: PD, pharmacology  
   **Calcium Channel** Blockers: AD, administration & dosage  
   **Calcium Channel** Blockers: AE, adverse effects  
   **Calcium Channel** Blockers: PK, pharmacokinetics  
 \***Calcium Channel** Blockers: PD, pharmacology  
   **Calcium Channels**: DE, drug effects  
   **Calcium Channels**: PH, physiology  
   **Heart Failure**, Congestive: DT, drug therapy  
 Humans  
   **Hypertension**: DT, drug therapy  
 Mibefradil  
 Muscle Contraction: DE, drug effects  
 Muscle, Smooth, Vascular: DE, drug effects  
 Muscle, Smooth, Vascular: PH, physiology  
 Randomized Controlled Trials  
 Tetrahydronaphthalenes: AD, administration & dosage  
 Tetrahydronaphthalenes: AE, adverse effects  
 Tetrahydronaphthalenes: PK, pharmacokinetics  
 \*Tetrahydronaphthalenes: PD, pharmacology  
 Vasodilator Agents: AD, administration & dosage  
 Vasodilator Agents: AE, adverse effects  
 Vasodilator Agents: PK, pharmacokinetics  
 \*Vasodilator Agents: PD, pharmacology  
 RN **116644-53-2** (Mibefradil)  
 CN 0 (Benzimidazoles); 0 (**Calcium Channel** Blockers); 0 (**Calcium Channels**); 0 (Tetrahydronaphthalenes); 0 (Vasodilator Agents)

L103 ANSWER 94 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN DUPLICATE 15  
 ACCESSION NUMBER: 1999:17587 TOXCENTER  
 DOCUMENT NUMBER: PubMed ID: 9884814  
 TITLE: Clinical pharmacokinetics of mibefradil  
 AUTHOR(S): Welker H A; Wiltshire H; Bullingham R  
 CORPORATE SOURCE: F. Hoffmann-La Roche, Basel, Switzerland.  
 Horst.Welker@Roche.com  
 SOURCE: Clinical pharmacokinetics, (1998 Dec) 35 (6) 405-23. Ref: 44.  
 Journal Code: 7606849. ISSN: 0312-5963.  
 COUNTRY: New Zealand  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
   **General Review; (REVIEW)**  
   (REVIEW, TUTORIAL)  
 FILE SEGMENT: MEDLINE  
 OTHER SOURCE: MEDLINE 1999100552  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 20011116  
   Last Updated on STN: 20011116

ED Entered STN: 20011116

Last Updated on STN: 20011116

AB Mibefradil, a tetralol derivative, is a new long-acting calcium antagonist used for the treatment of patients with **hypertension** and chronic stable **angina** pectoris. The drug is virtually completely metabolised, with less than 3% of an oral dose excreted unchanged in urine. Its metabolism occurs via parallel pathways, which fall into 2 broad categories: esterase-catalysed hydrolysis (producing the major plasma metabolite) and cytochrome P450 (CYP) 3A4-mediated oxidation. Plasma protein binding is greater than 99.5%, predominantly to alpha 1-acid glycoprotein. Oral multiple dose administration of mibefradil 50 or 100 mg once daily is associated with inhibition of the CYP3A4 pathway

of metabolism, increasing the half-life and bioavailability of the parent compound. The intensity of the inhibition of CYP similarly results in numerous clinically relevant drug interactions which ultimately motivated the voluntary withdrawal of mibefradil from the market. With multiple oral doses of 50 to 100 mg once daily, the time to maximum plasma concentration was approximately 2.4 hours, absolute bioavailability was around 80%, clearance was 5.7 to 7.5 L/h, oral terminal exponential volume of distribution was 180 L, and terminal exponential half-life was 22 hours (ranging between 17 and 25 hours). A NONMEM sparse data analysis indicated that apparent clearance is not affected by race, gender, age or bodyweight. Renal function does not affect the pharmacokinetics of mibefradil.

CT \*Benzimidazoles: PK, pharmacokinetics  
Benzimidazoles: TU, therapeutic use  
\*Calcium Channel Blockers: PK, pharmacokinetics  
Calcium Channel Blockers: TU, therapeutic use  
Cardiovascular Diseases: ME, metabolism  
Drug Interactions  
Food-Drug Interactions  
Humans  
Kidney Diseases: ME, metabolism  
Liver Diseases: ME, metabolism  
Mibefradil  
\*Tetrahydronaphthalenes: PK, pharmacokinetics  
Tetrahydronaphthalenes: TU, therapeutic use  
RN 116644-53-2 (Mibefradil)  
CN 0 (Benzimidazoles); 0 (Calcium Channel Blockers); 0  
(Tetrahydronaphthalenes)

L103 ANSWER 95 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN DUPLICATE 18  
ACCESSION NUMBER: 1998:39086 TOXCENTER  
DOCUMENT NUMBER: PubMed ID: 9607373  
TITLE: Mibefradil, a T-type channel-selective  
calcium antagonist: clinical trials in chronic  
stable angina pectoris  
AUTHOR(S): Massie B M  
CORPORATE SOURCE: University of California, San Francisco, USA  
SOURCE: American journal of hypertension : journal of the American  
Society of Hypertension, (1998 Apr) 11 (4 Pt 3) 95S-102S.  
Ref: 31.  
Journal Code: 8803676. ISSN: 0895-7061.  
COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
FILE SEGMENT: MEDLINE  
OTHER SOURCE: MEDLINE 1998268389  
LANGUAGE: English  
ENTRY DATE: Entered STN: 20011116  
Last Updated on STN: 20011116  
ED Entered STN: 20011116  
Last Updated on STN: 20011116  
AB Pharmacotherapy with nitrates, beta-blockers, and calcium antagonists is  
the cornerstone of management of patients with chronic stable  
angina pectoris. While these agents are all effective, their use  
may be limited by pharmacologic tolerance, side effects, and drug  
interactions. Mibefradil is a recently developed calcium antagonist with  
a unique chemical structure, pharmacologic profile, and mode of action.  
Unlike all previously available calcium antagonists, mibefradil acts  
primarily by selective blockade of T-type calcium

**channels**, rather than L-type channels, at clinically relevant concentrations. It has been evaluated as a treatment for **angina** in placebo-controlled and active-controlled clinical trials. Treatment with 50 mg mibefradil resulted in a significant improvement in exercise tolerance test duration in three of the five placebo-controlled trials, and a significant improvement in time to onset of **angina** in two of the five trials. Time to onset of **ischemia** as evaluated by 0.1 mV ST-segment depression was increased in all five placebo-controlled trials. Treatment with 100 mg mibefradil resulted in significant improvement in all three exercise tolerance test parameters in all studies. Mibefradil further improved exercise tolerance test duration and other efficacy parameters when administered concomitantly to patients on background beta-blocker or nitrate therapy. In addition, treatment with mibefradil was associated with a dose-dependent decrease in **heart** rate, double product, frequency of **anginal** attacks, nitroglycerin consumption, and both frequency and duration of silent **ischemic** episodes. In comparative trials, 100 mg mibefradil once daily was superior in efficacy to 10 mg amlodipine once daily and was at least equivalent to diltiazem in both efficacy and tolerability. Mibefradil was safe and well tolerated in all studies.

CT Check Tags: Comparative Study  
 Amlodipine: TU, therapeutic use  
 \***Angina** Pectoris: DT, drug therapy  
 Benzimidazoles: AE, adverse effects  
 \*Benzimidazoles: TU, therapeutic use  
 Calcium Channel Blockers: AE, adverse effects  
 \*Calcium Channel Blockers: TU, therapeutic use  
 Chronic Disease  
 Clinical Trials  
 Diltiazem: TU, therapeutic use  
 Humans  
 Mibefradil  
 Tetrahydronaphthalenes: AE, adverse effects  
 \*Tetrahydronaphthalenes: TU, therapeutic use  
 RN 116644-53-2 (Mibefradil)  
 42399-41-7 (Diltiazem)  
 88150-42-9 (Amlodipine)  
 CN 0 (Benzimidazoles); 0 (**Calcium Channel** Blockers); 0  
 (Tetrahydronaphthalenes)

L103 ANSWER 96 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN DUPLICATE 20

ACCESSION NUMBER: 1998:39085 TOXCENTER

DOCUMENT NUMBER: PubMed ID: 9607372

TITLE: Mibefradil, a T-channel-selective  
**calcium** antagonist: clinical trials in  
**hypertension**

AUTHOR(S): Oparil S

CORPORATE SOURCE: University of Alabama at Birmingham, 35294, USA

SOURCE: American journal of hypertension : journal of the American  
 Society of Hypertension, (1998 Apr) 11 (4 Pt 3) 88S-94S.  
 Ref: 30.

Journal Code: 8803676. ISSN: 0895-7061.

COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

**General Review; (REVIEW)**

(REVIEW, TUTORIAL)

FILE SEGMENT: MEDLINE

OTHER SOURCE: MEDLINE 1998268388

LANGUAGE: English

ENTRY DATE: Entered STN: 20011116



Last Updated on STN: 20011116

ED Entered STN: 20011116

Last Updated on STN: 20011116

AB Mibefradil, a tetralol derivative, is the first representative of a new class of calcium antagonists. It selectively blocks entry of calcium into cells through T-type channels. The efficacy and tolerability of mibefradil in the treatment of mild-to-moderate essential **hypertension** were evaluated in four placebo-controlled, double-blind, dose-finding studies involving over 1000 patients. Two trials involved patients from the general population, one examined a subpopulation of elderly patients, and one evaluated patients receiving chronic hydrochlorothiazide (HCTZ) treatment. Based on these studies, the recommended doses of mibefradil are 50 mg and 100 mg. Doses >100 mg/day were associated with small gains in efficacy and an increased incidence of adverse effects. Response (sitting diastolic blood pressure normalization to < or =90 mm Hg or reduction by > or =10 mm Hg) rates to mibefradil ranged from 46.0% to 68.6% with 50 mg, and from 60.0% to 93.2% with 100 mg. Normalization rates paralleled the response rates, ranging from 34.0% to 62.9% with 50 mg, and from 42.5% to 81.8% with 100 mg. The effects on sitting systolic blood pressure were similar. Treatment was associated with a slight, potentially beneficial reduction in **heart rate**. Results were similar across all populations, indicating that no dose adjustment is required for elderly and for HCTZ-treated patients. The frequency of adverse events was similar to that reported for placebo groups, with headache being the most common complaint. In comparative trials, mibefradil was more effective than nifedipine SR and diltiazem CD, and at least as effective as amlodipine and nifedipine GITS. Overall, mibefradil was better tolerated than the comparison drugs. Mibefradil, at the recommended doses of 50 to 100 mg/day, is safe and effective for the treatment of mild-to-moderate **hypertension**.

CT Check Tags: Comparative Study

\*Benzimidazoles: TU, therapeutic use

Blood Pressure: DE, drug effects

Calcium Channel Blockers: AE, adverse effects

\*Calcium Channel Blockers: TU, therapeutic use

Clinical Trials

Heart Rate: DE, drug effects

Humans

\*Hypertension: DT, drug therapy

Hypertension: PP, physiopathology

Mibefradil

\*Tetrahydronaphthalenes: TU, therapeutic use

RN 116644-53-2 (Mibefradil)

CN 0 (Benzimidazoles); 0 (Calcium Channel Blockers); 0 (Tetrahydronaphthalenes)

L103 ANSWER 97 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN DUPLICATE 22

ACCESSION NUMBER: 1998:33768 TOXCENTER

DOCUMENT NUMBER: PubMed ID: 9570425

TITLE: Potential **cardioprotective** effect of mibefradil in the long-term treatment of **hypertension**

AUTHOR(S): Waeber B

CORPORATE SOURCE: Division of Hypertension, CHUV, Lausanne, Switzerland

SOURCE: Cardiology, (1998) 89 Suppl 1 16-22. Ref: 34.

Journal Code: 1266406. ISSN: 0008-6312.

COUNTRY: Switzerland

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

FILE SEGMENT: MEDLINE

OTHER SOURCE: MEDLINE 1998230351  
LANGUAGE: English  
ENTRY DATE: Entered STN: 20011116  
Last Updated on STN: 20011116

ED Entered STN: 20011116

Last Updated on STN: 20011116

AB During the last 2 decades, remarkable progress has been made in the treatment of **hypertension** with the discovery of new drugs lowering blood pressure by various mechanisms, e.g. **calcium channel** blockers, angiotensin-converting enzyme inhibitors and angiotensin II antagonists. These **antihypertensive** agents are now widely used as first-line therapy although there is still no definite proof that they have a **cardioprotective** effect and reduce the mortality rate in patients with coronary **heart** disease. Mibefradil is a new calcium antagonist with a novel mechanism of action since it is the only drug available so far able to block T channels. This compound might be particularly effective in preventing **cardiac** morbidity and mortality. It reduces **heart** rate when lowering blood pressure, has no negative inotropic effect, allows regression of **cardiac** hypertrophy and is effective in the treatment of **angina**. Mibefradil produces a sustained blood pressure reduction with a close to optimal trough:peak ratio. A major advantage of this novel compound is its excellent tolerability over the dose range recommended (50-100 mg/day). In particular, leg edema is seen clearly less often during mibefradil treatment than during therapy with dihydropyridines. Mibefradil has therefore an attractive profile in terms of both efficacy and safety and represents a promising first-line option to treat **hypertensive** patients.

CT Benzimidazoles: PK, pharmacokinetics  
\*Benzimidazoles: TU, therapeutic use  
Blood Pressure: DE, drug effects  
Calcium Channel Blockers: PK, pharmacokinetics  
\*Calcium Channel Blockers: TU, therapeutic use  
Calcium Channels: DE, drug effects  
Calcium Channels: ME, metabolism  
Coronary Disease: ME, metabolism  
\*Coronary Disease: PC, prevention & control  
Drug Interactions  
Follow-Up Studies  
Heart Rate: DE, drug effects  
Humans  
\*Hypertension: DT, drug therapy  
Hypertension: ME, metabolism  
Mibefradil  
Safety  
Tetrahydronaphthalenes: PK, pharmacokinetics  
\*Tetrahydronaphthalenes: TU, therapeutic use  
Treatment Outcome  
RN 116644-53-2 (Mibefradil)  
CN 0 (Benzimidazoles); 0 (Calcium Channel Blockers); 0 (Calcium Channels); 0 (Tetrahydronaphthalenes)

L103 ANSWER 98 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN DUPLICATE 23

ACCESSION NUMBER: 1998:5003 TOXCENTER  
DOCUMENT NUMBER: PubMed ID: 9360806  
TITLE: Mibefradil (posicor)  
AUTHOR(S): Giles T D  
CORPORATE SOURCE: LSU Medical School, New Orleans, LA 70112, USA  
SOURCE: Comprehensive therapy, (1997 Nov) 23 (11) 761-3. Ref: 17.  
Journal Code: 7605837. ISSN: 0098-8243.

COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
FILE SEGMENT: MEDLINE  
OTHER SOURCE: MEDLINE 1998025281  
LANGUAGE: English  
ENTRY DATE: Entered STN: 20011116  
Last Updated on STN: 20011116

ED Entered STN: 20011116

Last Updated on STN: 20011116

CT \*Angina Pectoris: DT, drug therapy  
Benzimidazoles: AE, adverse effects  
\*Benzimidazoles: TU, therapeutic use  
Calcium Channel Blockers: AE, adverse effects  
\*Calcium Channel Blockers: TU, therapeutic use  
Clinical Trials  
Dose-Response Relationship, Drug  
Humans  
\*Hypertension: DT, drug therapy  
Mibefradil  
Tetrahydronaphthalenes: AE, adverse effects  
\*Tetrahydronaphthalenes: TU, therapeutic use  
Treatment Outcome  
RN 116644-53-2 (Mibefradil)  
CN 0 (Benzimidazoles); 0 (Calcium Channel Blockers); 0  
(Tetrahydronaphthalenes)

L103 ANSWER 99 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN DUPLICATE 28  
ACCESSION NUMBER: 1995:173807 TOXCENTER  
COPYRIGHT: Copyright 2005 ACS  
DOCUMENT NUMBER: CA12303025414J  
TITLE: Hemolysis on intravenous administration of a new calcium  
antagonist  
AUTHOR(S): Kleinbloesem, Cornelis H.; Siepmann, Martin; Kirch,  
Wilhelm  
CORPORATE SOURCE: Cent. Clinical Pharmacology, Clin-Pharma Research AG,  
Basel, Switz..  
SOURCE: Journal of Cardiovascular Pharmacology, (1995)  
Vol. 25, No. 6, pp. 855-8.  
CODEN: JPCPDT. ISSN: 0160-2446.  
COUNTRY: SWITZERLAND  
DOCUMENT TYPE: Journal  
FILE SEGMENT: CAPLUS  
OTHER SOURCE: CAPLUS 1995:614017  
LANGUAGE: English  
ENTRY DATE: Entered STN: 20011116  
Last Updated on STN: 20020903

ED Entered STN: 20011116

Last Updated on STN: 20020903

AB Hemolysis-inducing properties of the new calcium antagonist Ro 40-5967  
administered i.v. to 39 healthy male subjects were investigated in a  
placebo-controlled study. The volunteers were randomized into five  
parallel groups of 9 subjects each: three groups receiving infusions of 40  
mg Ro 40-5967 in 60, 30, and 15 min, resp.; one group receiving 80 mg Ro  
40-5967 in 30 min as two simultaneous doses of 40 mg in the cubital veins  
of both arms; and one group receiving 80 mg Ro 40-5967 in 30 min in one  
arm. Within each group, 3 subjects received placebo under randomized  
double-blind conditions. Plasma haptoglobin decreased by 67% after 3.5 h  
in 2 subjects who received 80 mg Ro 40-5967 in one arm (treatment schedule

thereupon discontinued). Serum bilirubin levels also increased in a dose-dependent manner in all groups as compared with placebo. Other parameters of hemolysis remained unchanged; no Hb-uria was observed "The intravascular hemolysis observed on infusion limits the therapeutic application of Ro 40-5967 to oral use only.

CC 1-8  
ST Miscellaneous Descriptors  
calcium antagonist Ro405967 hemolysis  
RN 116666-63-8

L103 ANSWER 100 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:1180 TOXCENTER  
COPYRIGHT: Copyright (c) 2005 The Thomson Corporation  
DOCUMENT NUMBER: 38-05044  
TITLE: Withdrawn drugs posed greater health risk for women than men, GAO says  
AUTHOR(S): anon  
SOURCE: American Journal of Health-System Pharmacy, (Mar 15 2001) Vol. 58, pp. 458, 462.  
CODEN: AHSPEK. ISSN: 1079-2082.  
DOCUMENT TYPE: Note  
FILE SEGMENT: IPA  
OTHER SOURCE: IPA 2001:5044  
LANGUAGE: English  
ENTRY DATE: Entered STN: 20011116  
Last Updated on STN: 20011116

ED Entered STN: 20011116

Last Updated on STN: 20011116

AB According to the General Accounting Office (GAO), women faced greater health risks than men from most of the prescription drugs withdrawn from the U.S. market in the past 4 yr: GAO noted that women have a higher incremental risk than men of arrhythmia after taking astemizole (Hismanal), cisapride (Propulsid), mibefradil dihydrochloride (Posicor), or terfenadine (Seldane). It was speculated that women's higher use of appetite suppressants fenfluramine hydrochloride (Pondimin) and dexfenfluramine hydrochloride (Redux), antidiabetic agent troglitazone (Rezulin), and gastrointestinal agent alosetron hydrochloride (Lotronex), compared with men's use, may have accounted for the greater health risk posed by these drugs.

Elvira deC. Weiss

SC 4 Toxicity; 22 Sociology, Economics and Ethics

CC 4:00 Antihistamines; 56:00 Gastrointestinal drugs; 24:04 Calcium antagonists; 4:00 Antihistamines; 28:20 Anorexics; 28:20 Anorexics; 68:20 Antidiabetic agents

ST Miscellaneous Descriptors

Astemizole; product withdrawal; toxicity, women  
Cisapride; product withdrawal; toxicity, women  
Mibefradil dihydrochloride; product withdrawal; toxicity, women  
Terfenadine; product withdrawal; toxicity, women  
Fenfluramine hydrochloride; product withdrawal; toxicity, women  
Dexfenfluramine hydrochloride; product withdrawal; toxicity, women  
Troglitazone; product withdrawal; toxicity, women  
Alosetron hydrochloride; product withdrawal; toxicity, women  
Product withdrawal; drugs; toxicity, women  
Toxicity; drugs; women  
Arrhythmia; drugs; toxicity, women  
Antihistamines; astemizole; product withdrawal  
Gastrointestinal drugs; cisapride; product withdrawal  
Calcium antagonists; mibefradil dihydrochloride; product withdrawal  
Antihistamines; terfenadine; product withdrawal

Anorexics; fenfluramine hydrochloride; product withdrawal  
 Anorexics; dexfenfluramine hydrochloride; product withdrawal  
 Antidiabetic agents; troglitazone; product withdrawal  
 Serotonin antagonists; alosetron hydrochloride; product withdrawal  
 Sex; patients; drug toxicity  
 Women; drugs; toxicity

RN 68844-77-9 (Astemizole)  
 81098-60-4 (Cisapride)  
 116666-63-8 (Mibefradil dihydrochloride)  
 50679-08-8 (Terfenadine)  
 404-82-0 (Fenfluramine hydrochloride)  
 3239-45-0 (Dexfenfluramine hydrochloride)  
 97322-87-7 (Troglitazone)  
 122852-69-1 (Alosetron hydrochloride)  
 CN Astemizole (Hismanal); Cisapride (Propulsid); Mibefradil dihydrochloride (Posicor); Terfenadine (Seldane); Fenfluramine hydrochloride (Pondimin); Dexfenfluramine hydrochloride (Redux); Troglitazone (Rezulin); Alosetron hydrochloride (Lotronex)

L103 ANSWER 101 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:59011 TOXCENTER  
 DOCUMENT NUMBER: PubMed ID: 11002855  
 TITLE: Calcium antagonists in the treatment of **heart** failure. Re-evaluation of therapeutic strategies  
 AUTHOR(S): Gattis W; O'Connor C M  
 CORPORATE SOURCE: Duke Clinical Research Institute, Durham, USA  
 SOURCE: Drugs, (2000) 59 Spec No 2 17-24. Ref: 22.  
 Journal Code: 7600076. ISSN: 0012-6667.  
 COUNTRY: New Zealand  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 FILE SEGMENT: MEDLINE  
 OTHER SOURCE: MEDLINE 2000450026  
 LANGUAGE: French  
 ENTRY DATE: Entered STN: 20011116  
 Last Updated on STN: 20011116

ED Entered STN: 20011116

Last Updated on STN: 20011116

AB The pharmacological management of **heart** failure has evolved during the last decade from therapies focused on improving haemodynamics to others that modulate neurohormonal systems which are activated in the setting of left ventricular dysfunction. Despite optimal inhibition of these systems with drugs such as ACE inhibitors, beta-blockers, digoxin and, most recently, spironolactone, the mortality rate remains unacceptably high. Calcium antagonists have long been investigated for use in a variety of **cardiovascular** diseases, including ischaemic **heart** disease, **hypertension**, and **heart** failure. However, concern has arisen with regard to the use of calcium antagonists in the treatment of left ventricular dysfunction--particularly those agents with negative inotropic activity. In addition, first generation dihydropyridines have also generated concern because of their profound vasodilatory effects and the fact that they have been shown to increase noradrenaline (norepinephrine) levels and neurohormonal activity. The third generation dihydropyridine calcium antagonists appear to be more promising therapies for **heart** failure, given their pharmacological properties of higher vascular selectivity and their minimal effects on neurohormonal activation. Several trials have been conducted with third generation dihydropyridines and additional trials are ongoing. A new class of calcium antagonists, which blocks the T-type

calcium channel, was introduced in 1998. The prototype drug, mibefradil, was rigorously tested for use in heart failure in the Mortality Assessment in Congestive Heart Failure (MACH-1) trial. It was expected that calcium antagonists blocking the T-type calcium channel would be of benefit, because of their lack of negative inotropic effects and their ability to induce regression of hypertrophy. The results of the MACH-1 trial were disappointing, and the trial was prematurely discontinued as a result of excess mortality in the mibefradil arm. The purpose of this review is to examine the evidence-based pharmacotherapeutic strategies in the management of heart failure, and to discuss current and potential roles for calcium antagonists in the therapeutic regimen.

CT    **Calcium Channel** Blockers: AE, adverse effects  
       \***Calcium Channel** Blockers: PD, pharmacology  
       **Calcium Channel** Blockers: TU, therapeutic use  
       Clinical Trials  
       English Abstract  
       Evidence-Based Medicine  
       \***Heart** Failure, Congestive: DT, drug therapy  
       Humans  
       Mibefradil: AE, adverse effects  
       \*Mibefradil: PD, pharmacology  
       Mibefradil: TU, therapeutic use  
       \*Ventricular Dysfunction, Left: DT, drug therapy  
 RN    116644-53-2 (Mibefradil)  
 CN    0 (**Calcium Channel** Blockers)

L103 ANSWER 102 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN  
 ACCESSION NUMBER: 2002:578840 TOXCENTER  
 DOCUMENT NUMBER: DART-TER-20001227  
 TITLE: Pregnancy and cardiovascular disease.  
 AUTHOR(S): Caulin-Glaser T; Setaro J F  
 CORPORATE SOURCE: Department of Medicine, Yale University School of  
                     Medicine, New Haven, CT.  
 SOURCE: Medical Complications During Pregnancy, (1999) 5  
           111-33. Ref: 207.  
           ISBN: 0-7216-7508-5.  
 DOCUMENT TYPE: (CHAPTER)  
                   (REVIEW, TUTORIAL)  
                   General Review; (REVIEW)  
 FILE SEGMENT: DART  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 20021200  
               Last Updated on STN: 20021200  
 ED    Entered STN: 20021200  
       Last Updated on STN: 20021200  
 CT    Check Tags: Human; Female  
       Pregnancy  
       \*Pregnancy Complications, Cardiovascular: TH, THERAPY  
       \*Pregnancy Complications, Cardiovascular: PP, PHYSIOPATHOLOGY  
       Hemodynamics  
       Heart Valve Prosthesis  
       Heart: DE, DRUG EFFECTS  
       Peripheral Vascular Diseases: TH, THERAPY  
       Heart Defects, Congenital: TH, THERAPY  
       Arrhythmia: TH, THERAPY  
       Rheumatic Heart Disease: TH, THERAPY  
       Coronary Disease: TH, THERAPY  
 RN    81-81-2 (Warfarin)  
       9005-49-6 (Heparin)

50-78-2 (Aspirin)  
58-32-2 (Dipyridamole)  
62571-86-2 (Captopril)  
75847-73-3 (Enalapril)  
76547-98-3 (Lisinopril)  
98048-97-6 (Fosinopril)  
85441-61-8 (Quinapril)  
86541-75-5 (Benazepril)  
56-54-2 (Quinidine)  
57-41-0 (Phenytoin)  
29122-68-7 (Atenolol)  
37350-58-6 (Metoprolol)  
1951-25-3 (Amiodarone)  
130350-52-6 (Ibutilide)  
21829-25-4 (Nifedipine)  
116666-63-8 (Mibefradil)  
51-61-6 (Dopamine)  
34368-04-2 (Dobutamine)  
60719-84-8 (Amrinone)  
78415-72-2 (Milrinone)  
51-43-4 (Epinephrine)  
51-41-2 (Norepinephrine)  
86-54-4 (Hydralazine)  
14402-89-2 (Sodium nitroprusside)  
525-66-6 (Propranolol)  
36894-69-6 (Labetalol)  
25812-30-0 (Gemfibrozil)  
59-67-6 (Niacin)  
75330-75-5 (Lovastatin)  
50925-79-6 (Colestipol)  
11041-12-6 (Cholestyramine)  
50-56-6 (Oxytocin)  
555-30-6 (Methyldopa)  
4205-90-7 (Clonidine)  
31828-71-4 (Mexiletine)  
54143-55-4 (Flecainide)  
54063-53-5 (Propafenone)

L103 ANSWER 103 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:1618 TOXCENTER

COPYRIGHT: Copyright (c) 2005 The Thomson Corporation

DOCUMENT NUMBER: 36-08019

TITLE: Safety of newly approved medicines: do recent market  
removals mean there is a problem?

AUTHOR(S): Friedman, M. A.; Woodcock, J.; Lumpkin, M. M.; Shuren, J.  
E.; Thompson, L. J.; et al

CORPORATE SOURCE: U.S. FDA, 5600 Fishers Ln., HF-28, Rockville, MD 20857,  
USA

SOURCE: Journal of the American Medical Association (USA), (  
May 12 1999) Vol. 281, pp. 1728-1734. 38 Refs.  
CODEN: JAMAAP. ISSN: 0098-7484.

DOCUMENT TYPE: Journal

FILE SEGMENT: IPA

OTHER SOURCE: IPA 1999:6787

LANGUAGE: English

ENTRY DATE: Entered STN: 20011116

Last Updated on STN: 20011116

ED Entered STN: 20011116

Last Updated on STN: 20011116

AB A study evaluating the relationship between changes in the U.S. Food and

Drug Administration (FDA) drug approval process and postmarketing surveillance and the recent withdrawal of 5 drug products is reported; the drug products evaluated were fenfluramine hydrochloride (Pondimin), dexfenfluramine hydrochloride (Redux), terfenadine (Seldane), mibefradil dihydrochloride (Posicor), and bromfenac sodium (Duract). When the withdrawn products were analyzed by date of approval, no increase in the number of drugs taken off the market was seen, demonstrating that reduced review processing time was not the reason for the cluster of removals.

Peggy L. Ruppel

SC 20 Legislation, Laws and Regulations; 4 Toxicity

CC 28:20 Anorexics; 28:20 Anorexics; 24:04 Cardiac drugs; 4:00

Antihistamines; 28:08.04 Anti-inflammatory agents

ST Miscellaneous Descriptors

Fenfluramine hydrochloride; product withdrawal; FDA approval process  
 Dexfenfluramine hydrochloride; product withdrawal; FDA approval process  
 Mibefradil dihydrochloride; product withdrawal; FDA approval process  
 Terfenadine; product withdrawal; FDA approval process  
 Bromfenac sodium; product withdrawal; FDA approval process  
 Drugs; approvals; product withdrawal  
 Product withdrawal; drugs; FDA approval process  
 Food and Drug Administration (U.S.); approvals; product withdrawal  
 Anorexics; fenfluramine hydrochloride; product withdrawal  
 Anorexics; dexfenfluramine hydrochloride; product withdrawal  
 Cardiac drugs; mibefradil dihydrochloride; product withdrawal  
 Antihistamines; terfenadine; product withdrawal  
 Anti-inflammatory agents; bromfenac sodium; product withdrawal  
 Administration; Food and Drug Administration; product withdrawal  
 Postmarketing surveillance; drugs; product withdrawal  
 Toxicity; drugs; product withdrawal

RN 404-82-0 (Fenfluramine hydrochloride)  
 3239-45-0 (Dexfenfluramine hydrochloride)  
 116666-63-8 (Mibefradil dihydrochloride)  
 50679-08-8 (Terfenadine)  
 120638-55-3 (Bromfenac sodium)

CN Fenfluramine hydrochloride (Pondimin); Dexfenfluramine hydrochloride (Redux); Terfenadine (Seldane); Mibefradil dihydrochloride (Posicor); Bromfenac sodium (Duract)

L103 ANSWER 104 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:4605 TOXCENTER

DOCUMENT NUMBER: PubMed ID: 10541773

TITLE: Drug-drug interactions of new active substances:  
 mibefradil example

COMMENT: Comment in: Eur J Clin Pharmacol. 2000 Jun;56(3):273.  
 PubMed ID: 10952485

AUTHOR(S): Krayenbuhl J C; Vozeh S; Kondo-Oestreicher M; Dayer P

CORPORATE SOURCE: Swiss Intercantonal Office for the Control of Medicines,  
 Berne, Switzerland

SOURCE: European journal of clinical pharmacology, (1999 Oct) 55  
 (8) 559-65. Ref: 37.

Journal Code: 1256165. ISSN: 0031-6970.

COUNTRY: GERMANY: Germany, Federal Republic of

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

**General Review; (REVIEW)**

(REVIEW, TUTORIAL)

FILE SEGMENT: MEDLINE

OTHER SOURCE: MEDLINE 2000009421

LANGUAGE: English

ENTRY DATE: Entered STN: 20011116

Last Updated on STN: 20011116



ED Entered STN: 20011116  
Last Updated on STN: 20011116

AB INTRODUCTION: Mibefradil was approved as a novel calcium antagonist in Switzerland in 1996. Following its launch as an **antihypertensive** and anti-**anginal** agent, there were reports about serious pharmacokinetic and pharmacodynamic interactions occurring with other drugs frequently administered to patients with **cardiovascular** diseases. Despite appropriate modifications of the prescribing information, such interactions continued to occur. The drug was finally withdrawn after a study in patients with congestive **heart** failure showed a trend to higher mortality with mibefradil. This increase in mortality could again be due to multiple interactions between mibefradil and other drugs. In retrospect, it can be concluded that several of the interactions, including the theoretical risk of severe toxicity in some patients, could have been and in fact were predicted on the basis of the data available before introduction to the market. Depending on the benefits, these problems would however not necessarily represent an unacceptable risk for a new active compound. RESULTS AND CONCLUSION: The most important points revealed by this analysis were: (1) when interpreting the results of interaction studies, it is important to consider not only the mean of the interaction effect but also the observed and the theoretically conceivable extreme effects in individual subjects and (2) a drug with a high interaction potential may represent a high risk even if an adequate warning is included in the product information. The need for specific pharmacokinetic and pharmacodynamic interaction studies with new drugs and the limitations of the pivotal clinical efficacy and safety studies during phase III in order to reveal such interactions are discussed.

CT \***Calcium Channel** Blockers: AE, adverse effects  
\***Calcium Channel** Blockers: PD, pharmacology  
Drug Approval  
Drug Interactions  
Humans  
\*Mibefradil: AE, adverse effects  
\*Mibefradil: PD, pharmacology  
Product Surveillance, Postmarketing  
Switzerland

RN 116644-53-2 (Mibefradil)  
CN 0 (**Calcium Channel** Blockers)

L103 ANSWER 105 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 1998:794 TOXCENTER  
COPYRIGHT: Copyright (c) 2005 The Thomson Corporation  
DOCUMENT NUMBER: 35-11094  
TITLE: Roche cites drug interactions in mibefradil withdrawal  
AUTHOR(S): anon  
SOURCE: American Journal of Health-System Pharmacy, (Jul 15 1998) Vol. 55, p. 1445.  
CODEN: AHSPEK. ISSN: 1079-2082.

DOCUMENT TYPE: Note  
FILE SEGMENT: IPA  
OTHER SOURCE: IPA 1998:2245  
LANGUAGE: English  
ENTRY DATE: Entered STN: 20011116  
Last Updated on STN: 20011116

ED Entered STN: 20011116  
Last Updated on STN: 20011116

AB It was reported that Roche Laboratories has voluntarily withdrawn mibefradil dihydrochloride (Posicor) from the market, citing the seriousness of its interactions with other drugs and the complexity of the

information that would be required for patients and prescribers to use the drug correctly.

Elvira deC. Weiss

SC 22 Sociology, Economics and Ethics; 7 Drug Interactions; 4 Toxicity

CC 24:04 Cardiac drugs

ST Miscellaneous Descriptors

Mibefradil dihydrochloride; product withdrawal; interactions

Product withdrawal; mibefradil dihydrochloride; interactions

Drug interactions; mibefradil dihydrochloride; product withdrawal

Toxicity; mibefradil dihydrochloride; product withdrawal

Cardiac drugs; mibefradil dihydrochloride; product withdrawal

Drug information; mibefradil dihydrochloride; product withdrawal

RN 116666-63-8 (Mibefradil dihydrochloride)

CN Mibefradil dihydrochloride (Posicor)

L103 ANSWER 106 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:920 TOXCENTER

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DOCUMENT NUMBER: 35-12458

TITLE: What lessons can be learned from withdrawal of mibefradil from the market?

AUTHOR(S): Li Wan Po, A.; Zhang, W. Y.

CORPORATE SOURCE: Ctr. for Evidence-Based Pharmacotherapy, Univ. of Nottingham, Nottingham NG7 2RD, England

SOURCE: Lancet (England), (Jun 20 1998) Vol. 351, pp. 1829-1830. 8 Refs.

CODEN: LANCAO. ISSN: 0023-7507.

DOCUMENT TYPE: Journal

FILE SEGMENT: IPA

OTHER SOURCE: IPA 1998:2735

LANGUAGE: English

ENTRY DATE: Entered STN: 20011116

Last Updated on STN: 20011116

ED Entered STN: 20011116

Last Updated on STN: 20011116

AB The withdrawal of the calcium antagonist, mibefradil dihydrochloride (Posicor), from the market by its manufacturer, Roche, due to new reports about serious interactions with other drugs is discussed, including information that can be learned from this experience.

Ellen Katz Neumann

SC 22 Sociology, Economics and Ethics; 4 Toxicity; 7 Drug Interactions

CC 24:04 Cardiac drugs

ST Miscellaneous Descriptors

Mibefradil dihydrochloride; product withdrawal; drug interactions

Cardiac drugs; mibefradil dihydrochloride; product withdrawal

Product withdrawal; mibefradil dihydrochloride; drug interactions

Drug interactions; mibefradil dihydrochloride; product withdrawal

Toxicity; mibefradil dihydrochloride; product withdrawal

RN 116666-63-8 (Mibefradil dihydrochloride)

CN Mibefradil dihydrochloride (Posicor)

L103 ANSWER 107 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:1541 TOXCENTER

COPYRIGHT: Copyright (c) 2005 The Thomson Corporation

DOCUMENT NUMBER: 36-01053

TITLE: Drug safety surfaces as a leading issue in policy making, coverage decisions

AUTHOR(S): Wechsler, J.

SOURCE: Formulary (USA), (Sep 1998) Vol. 33, pp. 910, 909.

CODEN: FORMF9. ISSN: 1082-801X.  
DOCUMENT TYPE: Journal  
FILE SEGMENT: IPA  
OTHER SOURCE: IPA 1998:5134  
LANGUAGE: English  
ENTRY DATE: Entered STN: 20011116  
Last Updated on STN: 20011116  
ED Entered STN: 20011116  
Last Updated on STN: 20011116  
AB The question of whether the U. S. Food and Drug Administration (FDA) has compromised public safety by allowing speedy drug approvals of products such as sildenafil citrate (Viagra), mibefradil dihydrochloride (Posicor), bromfenac sodium (Duract), fenfluramine, and dexfenfluramine by the pharmaceutical manufacturer is discussed.  
Brenda L. Ward  
SC 20 Legislation, Laws and Regulations; 4 Toxicity  
CC 24:12 Vasodilating agents; 28:08.04 Anti-inflammatory agents; 24:04 Cardiac drugs; 28:20 Anorexics; 28:20 Anorexics  
ST Miscellaneous Descriptors  
Mibefradil dihydrochloride; approvals; FDA  
Sildenafil citrate; approvals; FDA  
Bromfenac sodium; approvals; FDA  
Fenfluramine; approvals; FDA  
Dexfenfluramine; approvals; FDA  
Regulations; Food and Drug Administration; drug approval process  
Drugs, investigational; approvals; FDA  
Industry, pharmaceutical; regulations; drug approval process  
Vasodilating agents; sildenafil citrate; FDA approval  
Anti-inflammatory agents; bromfenac sodium; FDA approval  
Cardiac drugs; mibefradil dihydrochloride; FDA approval  
Anorexics; fenfluramine; FDA approval  
Anorexics; dexfenfluramine; FDA approval  
RN 116666-63-8 (Mibefradil dihydrochloride)  
171599-83-0 (Sildenafil citrate)  
120638-55-3 (Bromfenac sodium)  
458-24-2 (Fenfluramine)  
3239-44-9 (Dexfenfluramine)  
CN Mibefradil dihydrochloride (Posicor); Sildenafil citrate (Viagra);  
Bromfenac sodium (Duract)

L103 ANSWER 108 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 1999:77644 TOXCENTER  
COPYRIGHT: Copyright (c) 2005 The Thomson Corporation  
DOCUMENT NUMBER: PREV199900132666  
TITLE: Mibefradil (Posicor) induced sinus arrest  
AUTHOR(S): Sanders, P. [Reprint author]; Walker, J.; Craig, R. J.;  
Hill, J. T. Y.; Steele, P. M.  
CORPORATE SOURCE: Cardiovascular Invest. Unit, Royal Adelaide Hosp., North  
Terrace, Adelaide, SA 5000, Australia  
SOURCE: Australian and New Zealand Journal of Medicine, (Dec., 1998) Vol. 28, No. 6, pp. 836-837. print.  
CODEN: ANZJB8. ISSN: 0004-8291.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BIOSIS  
OTHER SOURCE: BIOSIS 1999:132666  
LANGUAGE: English  
ENTRY DATE: Entered STN: 20011116  
Last Updated on STN: 20011116  
ED Entered STN: 20011116  
Last Updated on STN: 20011116

CC Toxicology - General and methods 22501  
 Cardiovascular system - General and methods 14501  
 Pharmacology - General 22002  
 CT Hypertension  
 ST Major Concepts  
 Cardiovascular Medicine (Human Medicine, Medical Sciences); Toxicology  
 ST Diseases  
 essential hypertension: vascular disease  
 Hypertension (MeSH)  
 ST Diseases  
 sinus arrest: heart disease, toxicity, induced  
 ST Chemicals & Biochemicals  
 calcium-ion channels: L-type, T-type; mibefradil [posicor]:  
 antihypertensive-drug  
 ST Miscellaneous Descriptors  
 Case Study  
 ORGN Classifier  
 Hominidae 86215  
 Super Taxa  
 Primates; Mammalia; Vertebrata; Chordata; Animalia  
 Organism Name  
 human: patient  
 Taxa Notes  
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates  
 RN 116644-53-2 (mibefradil)  
 116644-53-2 (posicor)  
 14127-61-8 (CALCIUM-ION)  
 116666-63-8 (POSICOR)

L103 ANSWER 109 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:24954 TOXCENTER  
 DOCUMENT NUMBER: PubMed ID: 9506192  
 TITLE: Use of **calcium channel** blockers in  
**hypertension**  
 AUTHOR(S): Conlin P R; Williams G H  
 CORPORATE SOURCE: Harvard Medical School, Boston, Massachusetts, USA  
 SOURCE: Advances in internal medicine, (1998) 43 533-62. Ref: 102.  
 Journal Code: 0370427. ISSN: 0065-2822.  
 COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
**General Review; (REVIEW)**  
 (REVIEW, TUTORIAL)  
 FILE SEGMENT: MEDLINE  
 OTHER SOURCE: MEDLINE 1998167092  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 20011116  
 Last Updated on STN: 20011116

ED Entered STN: 20011116

Last Updated on STN: 20011116

AB During the past 20 years the number of subclasses of **calcium channel** blockers has increased from one to four. Three classes have only a single clinically approved compound: verapamil, diltiazem, and mibefradil. The fourth class, dihydropyridines, contains numerous compounds. All agents are effective in lowering blood pressure in short-term studies, and side effects that trouble the patient are infrequent. Long-term studies in **hypertensive** patients are limited. Short-acting agents such as nifedipine have been associated with an increased **cardiovascular** risk in some, but not all studies. These agents also probably create a compliance problem for **hypertensive** patients because of the need for multiple daily doses

and their unpleasant side effects, e.g., ankle edema, palpitations, and flushing. Therefore, they are not useful or indicated for the treatment of **hypertensive** patients. No data have suggested that long-acting dihydropyridines or nondihydropyridine **calcium channel** blockers share the same fate. Indeed, several lines of evidence suggest the opposite: they have a **cardioprotective** effect. However, definitive information will require the completion of several long-term trials, including ALLHAT, CONVINCENCE, HOT, INSIGHT and NORDIL. Finally, it is important to reflect on the lessons learned from the controversy associated with the potential risks of **calcium channel** blockers. First, disagreements are common when one uses case-controlled studies and are reflective of the poor precision of the methods used. What is statistically relevant in one study may not hold true for another and may have no clinical relevance, particularly if the relative risk is less than 2. Investigators need to temper their enthusiasm to reflect this reality. Second, at the cutting edge of science there is probably relatively little agreement about what is correct among equally competent scientists. All have bias in their positions and should both recognize and admit so to themselves and their colleagues. Inferring that those who disagree have an unstated secondary agenda that will bring personal financial rewards or government accolades is inappropriate and counterproductive. Third, the randomized clinical trial, despite all its imperfections, is still the best tool to establish common ground on controversial issues. Finally, what may seem best from the public health perspective may not be in the best interest of the individual patient--a possibility that physicians have to constantly consider. For example, no public health benefit occurs if patients remain **hypertensive** because they fail to take their medications, no matter what the medication.

CT    **Antihypertensive** Agents: AE, adverse effects  
       **Antihypertensive** Agents: CL, classification  
       \***Antihypertensive** Agents: TU, therapeutic use  
       Benzimidazoles: TU, therapeutic use  
       Blood Pressure: DE, drug effects  
       **Calcium Channel** Blockers: AE, adverse effects  
       **Calcium Channel** Blockers: CL, classification  
       \***Calcium Channel** Blockers: TU, therapeutic use  
       Case-Control Studies  
       Clinical Trials  
       Dihydropyridines: TU, therapeutic use  
       Diltiazem: TU, therapeutic use  
       **Heart** Diseases: ET, etiology  
       **Heart** Diseases: PC, prevention & control  
       Humans  
       \***Hypertension**: DT, drug therapy  
       Longitudinal Studies  
       Mibefradil  
       Nifedipine: AE, adverse effects  
       Nifedipine: TU, therapeutic use  
       Public Health  
       Randomized Controlled Trials  
       Risk Factors  
       Tetrahydronaphthalenes: TU, therapeutic use  
       Vasodilator Agents: AE, adverse effects  
       Vasodilator Agents: TU, therapeutic use  
       Verapamil: TU, therapeutic use  
 RN    116644-53-2 (Mibefradil)  
       21829-25-4 (Nifedipine)  
       42399-41-7 (Diltiazem)  
       52-53-9 (Verapamil)

CN 0 (Antihypertensive Agents); 0 (Benzimidazoles); 0 (Calcium Channel Blockers); 0 (Dihydropyridines); 0 (Tetrahydronaphthalenes); 0 (Vasodilator Agents)

L103 ANSWER 110 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:94 TOXCENTER  
COPYRIGHT: Copyright (c) 2005 The Thomson Corporation  
DOCUMENT NUMBER: 36-01532  
TITLE: 1998 New drug review  
AUTHOR(S): Wick, J.  
CORPORATE SOURCE: District of Columbia's Dept. of Human Serv., Washington, DC, USA  
SOURCE: Consultant Pharmacist (USA), (Apr 1998) Vol. 13, pp. 346-348, 350, 352, 354, 356-358, 361, 365-366, 368. CODEN: CNPHEB. ISSN: 0888-5109.  
DOCUMENT TYPE: Journal  
FILE SEGMENT: IPA  
OTHER SOURCE: IPA 1999:300  
LANGUAGE: English  
ENTRY DATE: Entered STN: 20011116  
Last Updated on STN: 20011116

ED Entered STN: 20011116

Last Updated on STN: 20011116

AB An overview is presented of 16 new drugs of 1997: alatrofloxacin (I.V. Trovan), delavirdine (Rescriptor), eprosartan mesylate (Teveten), fenoldopam mesylate (Corlopam), grepafloxacin hydrochloride (Raxar), irbesartan (Avapro), mibefradil dihydrochloride (Posicor), nelfinavir (Viracept), pramipexole dihydrochloride (Mirapex), quetiapine fumarate (Seroquel), repaglinide (Prandin), ropinirole hydrochloride (Requip), saquinavir mesylate (Fortovase), tolcapone (Tasmar), troglitazone (Rezulin), and trovafloxacin mesylate (Trovan); these drugs were selected by long-term care pharmacists from practices across the country as being the drugs about which they were most curious. The mechanism of action, adverse reactions, drug interactions, pharmacokinetics, monitoring tips, and dosing of these drugs are presented along with a list of the other agents approved in 1997 but not included in the overview. A discussion of the possible approval of the previously withdrawn thalidomide is also presented.

Lisa Webster

SC 11 Pharmacology; 6 Drug Evaluations; 15 Drug Metabolism and Body Distribution; 4 Toxicity

CC 28:08.04 Anti-inflammatory agents; 8:22 Quinolones; 24:08 Hypotensive agents; 24:08 Hypotensive agents; 8:22 Quinolones; 24:08 Hypotensive agents; 24:04 Cardiac drugs; 12:08.04 Antiparkinson agents; 68:20 Antidiabetic agents; 12:08.04 Antiparkinson agents; 12:08.04 Antiparkinson agents; 68:20 Antidiabetic agents; 8:22 Quinolones

ST Miscellaneous Descriptors

Thalidomide; approvals; discussion  
Alatrofloxacin; overview  
Delavirdine; overview  
Eprosartan mesylate; overview  
Fenoldopam mesylate; overview  
Grepafloxacin hydrochloride; overview  
Irbesartan; overview  
Mibefradil dihydrochloride; overview  
Nelfinavir; overview  
Pramipexole dihydrochloride; overview  
Quetiapine fumarate; overview  
Repaglinide; overview  
Ropinirole hydrochloride; overview

3/4

Saquinavir mesylate; overview  
 Tolcapone; overview  
 Troglitazone; overview  
 Trovafloxacin mesylate; overview  
 Drugs; new; 1997  
 Drugs, investigational; approvals; 1997  
 Anti-inflammatory agents; thalidomide; approvals  
 Dosage; new drugs; 1997  
 Toxicity; new drugs; 1997  
 Drug interactions; new drugs; 1997  
 Mechanism of action; new drugs; 1997  
 Pharmacokinetics; new drugs; 1997  
 Quinolones; alatrofloxacin; overview  
 Antiretroviral agents; delavirdine; overview  
 Hypotensive agents; eprosartan mesylate; overview  
 Hypotensive agents; fenoldopam mesylate; overview  
 Quinolones; grepafloxacin hydrochloride; overview  
 Hypotensive agents; irbesartan; overview  
 Cardiac drugs; mibefradil dihydrochloride; overview  
 Antiretroviral agents; nelfinavir; overview  
 Antiparkinson agents; pramipexole dihydrochloride; overview  
 Antipsychotic agents; quetiapine fumarate; overview  
 Antidiabetic agents; repaglinide; overview  
 Antiparkinson agents; ropinirole hydrochloride; overview  
 Antiretroviral agents; saquinavir mesylate; overview  
 Antiparkinson agents; tolcapone; overview  
 Antidiabetic agents; troglitazone; overview  
 Quinolones; trovafloxacin mesylate; overview

- RN 50-35-1 (Thalidomide)  
 157182-32-6 (Alatrofloxacin)  
 136817-59-9 (Delavirdine)  
 144143-96-4 (Eprosartan mesylate)  
 67227-57-0 (Fenoldopam mesylate)  
 161967-81-3 (Grepafloxacin hydrochloride)  
 138402-11-6 (Irbesartan)  
 116666-63-8 (Mibefradil dihydrochloride)  
 159989-64-7 (Nelfinavir)  
 104632-25-9 (Pramipexole dihydrochloride)  
 111974-72-2 (Quetiapine fumarate)  
 135062-02-1 (Repaglinide)  
 91374-20-8 (Ropinirole hydrochloride)  
 149845-06-7 (Saquinavir mesylate)  
 134308-13-7 (Tolcapone)  
 97322-87-7 (Troglitazone)  
 147059-75-4 (Trovafloxacin mesylate)  
 CN Alatrofloxacin (Trovan I.V.); Delavirdine (Rescriptor); Eprosartan mesylate (Teveten); Fenoldopam mesylate (Corlopam); Grepafloxacin hydrochloride (Raxar); Irbesartan (Avapro); Mibefradil dihydrochloride (Posicor); Nelfinavir (Viracept); Pramipexole dihydrochloride (Mirapex); Quetiapine fumarate (Seroquel); Repaglinide (Prandin); Ropinirole hydrochloride (Requip); Saquinavir mesylate (Fortovase); Tolcapone (Tasmar); Troglitazone (Rezulin); Trovafloxacin mesylate (Trovan)

L103 ANSWER 111 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:567 TOXCENTER

COPYRIGHT: Copyright (c) 2005 The Thomson Corporation

DOCUMENT NUMBER: 35-09366

TITLE: Diazepam rectal gel and mibefradil dihydrochloride

AUTHOR(S): Levien, T.; Baker, D. E.

CORPORATE SOURCE: Coll. of Pharm., Washington State Univ., 601 W. First

SOURCE: Ave., Spokane, WA 99201-3899, USA  
Hospital Pharmacy (USA), (Mar 1998) Vol. 33, pp.  
302, 304-306, 309-312, 314-319. 28 Refs.  
CODEN: HOPHAZ. ISSN: 0018-5787.

DOCUMENT TYPE: Journal  
FILE SEGMENT: IPA  
OTHER SOURCE: IPA 1998:1661  
LANGUAGE: English  
ENTRY DATE: Entered STN: 20011116  
Last Updated on STN: 20011116

ED Entered STN: 20011116  
Last Updated on STN: 20011116

AB An overview of mibefradil dihydrochloride (Posicor) and a rectal gel of diazepam (Diastat) is presented, including the indications, mechanism of action, pharmacokinetics, contraindications, warnings, precautions, adverse reactions, drug interactions, recommended monitoring, dosage and administration, and product availability; clinical studies of the use of diazepam rectal gel in the treatment of epileptic seizures and mibefradil in the treatment of hypertension, chronic stable angina pectoris, and congestive heart failure are considered. This article qualifies for 2 hours U.S. CE credit by the ACPE.  
Ramune T. Dailide

SC 11 Pharmacology; 6 Drug Evaluations; 8 Biopharmaceutics; 15 Drug Metabolism and Body Distribution

CC 28:12 Anticonvulsants; 24:04 Calcium antagonists

ST Miscellaneous Descriptors  
Diazepam; epilepsy; rectal gels  
Mibefradil dihydrochloride; overview  
CE credit; diazepam rectal gels, mibefradil dihydrochloride  
Anticonvulsants; diazepam; rectal gels  
Calcium antagonists; mibefradil dihydrochloride; overview  
Mechanism of action; diazepam; rectal gels  
Mechanism of action; mibefradil dihydrochloride; overview  
Pharmacokinetics; diazepam; rectal gels  
Pharmacokinetics; mibefradil dihydrochloride; overview  
Contraindications; diazepam; rectal gels  
Contraindications; mibefradil dihydrochloride; overview  
Toxicity; diazepam; rectal gels  
Toxicity; mibefradil dihydrochloride; overview  
Drug interactions; diazepam; rectal gels  
Drug interactions; mibefradil dihydrochloride; overview  
Dosage; diazepam; rectal gels  
Dosage; mibefradil dihydrochloride; overview  
Dosage schedules; diazepam; rectal gels  
Dosage schedules; mibefradil dihydrochloride; overview  
Drug administration; diazepam; rectal gels  
Drug administration; mibefradil dihydrochloride; overview  
Clinical studies; diazepam; rectal gels  
Clinical studies; mibefradil dihydrochloride; overview  
Epilepsy; diazepam; rectal gels  
Hypertension; mibefradil dihydrochloride; overview  
Angina pectoris; mibefradil dihydrochloride; overview  
Heart failure; mibefradil dihydrochloride; congestive  
Drug administration routes; rectal; diazepam  
Dosage forms; diazepam; rectal gels  
Gels; diazepam; rectal

RN 439-14-5 (Diazepam)  
116666-63-8 (Mibefradil dihydrochloride)

CN Diazepam (Diastat); Mibefradil dihydrochloride (Posicor)



L103 ANSWER 112 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:96 TOXCENTER  
COPYRIGHT: Copyright (c) 2005 The Thomson Corporation  
DOCUMENT NUMBER: 36-01540  
TITLE: Compliance problems taken to heart  
AUTHOR(S): Sutherland, K.  
SOURCE: Australian Journal of Pharmacy (Australia), (Mar 1998) Vol. 79, pp. 246-247, 250, 252.  
CODEN: AJPRBM. ISSN: 0311-8002.  
DOCUMENT TYPE: Journal  
FILE SEGMENT: IPA  
OTHER SOURCE: IPA 1999:308  
LANGUAGE: English  
ENTRY DATE: Entered STN: 20011116  
Last Updated on STN: 20011116

ED Entered STN: 20011116

Last Updated on STN: 20011116

AB A brief overview of drugs recently launched in Australia for the treatment of hypercholesterolemia (atorvastatin calcium), hypertension (losartan potassium (Cozaar) and mibefradil dihydrochloride (Posicor)), and angina pectoris (mibefradil dihydrochloride) is presented; it was noted that the low side effect profile, high tolerability, and convenient dosing of each drug should help to improve patient compliance.

Wanda Hicks

SC 11 Pharmacology; 6 Drug Evaluations; 4 Toxicity

CC 24:06 Antilipemic agents; 24:08 Hypotensive agents; 24:04 Cardiac drugs

ST Miscellaneous Descriptors

Atorvastatin calcium; hypercholesterolemia; overview  
Losartan potassium; hypertension; overview  
Mibefradil dihydrochloride; hypertension; overview  
Antilipemic agents; atorvastatin calcium; hypercholesterolemia  
Hypotensive agents; losartan potassium; hypertension  
Cardiac drugs; mibefradil dihydrochloride; overview  
Hypercholesterolemia; atorvastatin calcium; overview  
Hypertension; losartan potassium; overview  
Hypertension; mibefradil dihydrochloride; overview  
Angina pectoris; mibefradil dihydrochloride; overview  
Compliance; patients; cardiovascular drugs  
Toxicity; atorvastatin calcium; overview  
Toxicity; losartan potassium; overview  
Toxicity; mibefradil dihydrochloride; overview  
Dosage; atorvastatin calcium; overview  
Dosage; losartan potassium; overview  
Dosage; mibefradil dihydrochloride; overview  
Australia; new drugs; overview  
Drugs; new; Australia

RN 134523-03-8 (Atorvastatin calcium)

124750-99-8 (Losartan potassium)

116666-63-8 (Mibefradil dihydrochloride)

CN Losartan potassium (Cozaar); Mibefradil dihydrochloride (Posicor)

L103 ANSWER 113 OF 198 TOXCENTER COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:1286 TOXCENTER  
COPYRIGHT: Copyright (c) 2005 The Thomson Corporation  
DOCUMENT NUMBER: 35-14269  
TITLE: New drug review  
AUTHOR(S): Riley, T. N.; DeRuiter, J.  
CORPORATE SOURCE: Sch. of Pharm., Auburn Univ., Auburn, AL, USA  
SOURCE: US Pharmacist (USA), (Mar 1998) Vol. 23, pp. 165-186, 189-190. 52 Refs.

CODEN: USPHD5. ISSN: 0148-4818.  
 DOCUMENT TYPE: Journal  
 FILE SEGMENT: IPA  
 OTHER SOURCE: IPA 1998:4127  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 20011116  
 Last Updated on STN: 20011116

ED Entered STN: 20011116

Last Updated on STN: 20011116

AB The development, pharmacology, mechanism of action, results of clinical studies, toxicity, drug interactions, pharmacokinetics, dosage, and drug administration of newly approved drugs by the U.S. Food and Drug Administration (FDA), including pramipexole dihydrochloride (Mirapex) and ropinirole hydrochloride (Requip) for Parkinson disease, bromfenac sodium (Duract) for pain relief, grepafloxacin hydrochloride (Raxar) for respiratory tract infections, irbesartan (Avapro) for hypertension, mibefradil dihydrochloride (Posicor) for hypertension and chronic stable angina, quetiapine fumarate (Seroquel) for schizophrenia, raloxifene hydrochloride (Evista) for menopause symptoms, and zolmitriptan (Zomig) for migraines, are discussed. This article qualifies for 4 hours U.S. CE credit by the ACPE.

Elizabeth G. Rudnic

SC 11 Pharmacology; 6 Drug Evaluations; 4 Toxicity

CC 28:08.04 Anti-inflammatory agents; 8:22 Quinolones; 24:08 Hypotensive agents; 24:04 Cardiac drugs; 12:08.04 Antiparkinson agents; 68:16 Estrogens; 12:08.04 Antiparkinson agents

ST Miscellaneous Descriptors

Pramipexole dihydrochloride; Parkinson disease

Ropinirole hydrochloride; Parkinson disease

Bromfenac sodium; pain

Grepafloxacin hydrochloride; respiratory tract infections

Irbesartan; hypertension

Mibefradil dihydrochloride; hypertension

Quetiapine fumarate; schizophrenia

Raloxifene hydrochloride; menopause

Zolmitriptan; migraine

CE credit; new drugs

Pain; bromfenac sodium

Respiratory tract infections; grepafloxacin hydrochloride

Hypertension; irbesartan

Hypertension; mibefradil dihydrochloride

Angina pectoris; mibefradil

Parkinson disease; pramipexole dihydrochloride

Parkinson disease; ropinirole hydrochloride

Schizophrenia; quetiapine fumarate

Menopause; raloxifene hydrochloride

Migraine; zolmitriptan

Food and Drug Administration (U.S.); approvals; 1998

Drugs; new; 1998 approvals

Mechanism of action; bromfenac sodium; pain

Mechanism of action; grepafloxacin hydrochloride; respiratory tract infections

Mechanism of action; irbesartan; hypertension

Mechanism of action; mibefradil dihydrochloride; hypertension

Mechanism of action; pramipexole dihydrochloride; Parkinson disease

Mechanism of action; quetiapine fumarate; schizophrenia

Mechanism of action; raloxifene hydrochloride; menopause

Mechanism of action; ropinirole hydrochloride; Parkinson disease

Mechanism of action; zolmitriptan; migraine

Clinical studies; bromfenac sodium; pain

Clinical studies; grepafloxacin hydrochloride; respiratory tract infections  
Clinical studies; irbesartan; hypertension  
Clinical studies; mibefradil dihydrochloride; hypertension  
Clinical studies; pramipexole dihydrochloride; Parkinson disease  
Clinical studies; quetiapine fumarate; schizophrenia  
Clinical studies; raloxifene hydrochloride; menopause  
Clinical studies; ropinirole hydrochloride; Parkinson disease  
Clinical studies; zolmitriptan; migraine  
Toxicity; bromfenac sodium  
Toxicity; grepafloxacin hydrochloride  
Toxicity; irbesartan  
Toxicity; mibefradil dihydrochloride  
Toxicity; pramipexole dihydrochloride  
Toxicity; quetiapine fumarate  
Toxicity; raloxifene hydrochloride  
Toxicity; ropinirole hydrochloride  
Toxicity; zolmitriptan  
Drug interactions; bromfenac sodium  
Drug interactions; grepafloxacin hydrochloride  
Drug interactions; irbesartan  
Drug interactions; mibefradil dihydrochloride  
Drug interactions; pramipexole dihydrochloride  
Drug interactions; quetiapine fumarate  
Drug interactions; raloxifene hydrochloride  
Drug interactions; ropinirole hydrochloride  
Drug interactions; zolmitriptan  
Dosage; bromfenac sodium; pain  
Dosage; grepafloxacin hydrochloride; respiratory tract infections  
Dosage; irbesartan; hypertension  
Dosage; mibefradil dihydrochloride; hypertension  
Dosage; pramipexole dihydrochloride; Parkinson disease  
Dosage; quetiapine fumarate; schizophrenia  
Dosage; raloxifene hydrochloride; menopause  
Dosage; ropinirole hydrochloride; Parkinson disease  
Dosage; zolmitriptan; migraine  
Pharmacokinetics; bromfenac sodium  
Pharmacokinetics; grepafloxacin hydrochloride  
Pharmacokinetics; irbesartan  
Pharmacokinetics; mibefradil dihydrochloride  
Pharmacokinetics; pramipexole dihydrochloride  
Pharmacokinetics; quetiapine fumarate  
Pharmacokinetics; raloxifene hydrochloride  
Pharmacokinetics; ropinirole hydrochloride  
Pharmacokinetics; zolmitriptan  
Drug administration; bromfenac sodium  
Drug administration; grepafloxacin hydrochloride  
Drug administration; irbesartan  
Drug administration; mibefradil dihydrochloride  
Drug administration; pramipexole dihydrochloride  
Drug administration; quetiapine fumarate  
Drug administration; raloxifene hydrochloride  
Drug administration; ropinirole hydrochloride  
Drug administration; zolmitriptan; migraine  
Anti-inflammatory agents; bromfenac sodium; pain  
Quinolones; grepafloxacin hydrochloride; respiratory tract infections  
Hypotensive agents; irbesartan; hypertension  
Cardiac drugs; mibefradil dihydrochloride; hypertension  
Antiparkinson agents; pramipexole dihydrochloride; Parkinson disease  
Antipsychotic agents; quetiapine fumarate; schizophrenia

Estrogens; raloxifene hydrochloride; menopause  
 Antiparkinson agents; ropinirole hydrochloride; Parkinson disease  
 Serotonin agonists; zolmitriptan; migraine

L103 ANSWER 132 OF 198 MEDLINE on STN  
 ACCESSION NUMBER: 2000497441 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 10882031  
 TITLE: Pharmacodynamic interaction between **mibefradil**  
 and other **calcium channel** blockers.  
 AUTHOR: Matthes J; Huber I; Haaf O; Antepohl W; Striessnig J;  
 Herzig S  
 CORPORATE SOURCE: Department of Pharmacology, University of Koln, Germany.  
 SOURCE: Naunyn-Schmiedeberg's archives of pharmacology, (2000  
 Jun) 361 (6) 578-83.  
 Journal code: 0326264. ISSN: 0028-1298.  
 PUB. COUNTRY: GERMANY: Germany, Federal Republic of  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200010  
 ENTRY DATE: Entered STN: 20001027  
 Last Updated on STN: 20001027  
 Entered Medline: 20001019  
 ED Entered STN: 20001027  
 Last Updated on STN: 20001027  
 Entered Medline: 20001019  
 AB Briefly after withdrawal of the (T-type) **calcium channel**  
 blocker **mibefradil** from the market, four cases of  
 life-threatening interaction of mibefradil with dihydropyridines were  
 reported. We investigated in vitro whether mibefradil interacts with a  
 dihydropyridine, as described for other non-dihydropyridine compounds.  
 Rat working **hearts** were used to examine functional interactions  
 between amlodipine and **mibefradil**. Gallopamil and another  
 T-type-channel blocker, ethosuximide, were included for comparison.  
 Effects of mibefradil, (+)- and (-)-gallopamil on [3H](+)-isradipine  
 binding were studied in membranes from tsA201-cells transfected with  
 alpha(1c)-, alpha(2)delta-, and beta(1a)- or beta(2a)-calcium channel  
 subunits. Mibefradil increased negative inotropic effect of amlodipine,  
 but not of gallopamil. Gallopamil and ethosuximide showed no influence on  
 contractile effects of amlodipine. Furthermore, mibefradil  
 concentration-dependently caused bradycardic rhythm disturbance. The same  
 type of **arrhythmia** was observed combining low concentrations of  
**mibefradil** with amlodipine, or with gallopamil, respectively.  
 Amlodipine alone, or the combination of gallopamil or ethosuximide with  
 amlodipine did not cause any arrhythmia. Binding studies showed a  
 concentration-dependent positive allosteric interaction between  
 [3H](+)-isradipine and mibefradil, but not with [3H](+)-isradipine and  
 gallopamil enantiomers. Molecular and functional evidence points to an  
 interaction between a dihydropyridine and mibefradil. Mibefradil caused  
 rhythm disturbances and potentiation of negative inotropy when combined  
 with amlodipine.  
 CT Check Tags: Female; In Vitro; Male  
 Amlodipine: PD, pharmacology  
 Animals  
 \*Arrhythmia: CI, chemically induced  
 Calcium Channel Blockers: ME, metabolism  
 \*Calcium Channel Blockers: PD, pharmacology  
 \*Calcium Channels, L-Type: DE, drug effects  
 Calcium Channels, L-Type: GE, genetics  
 Cell Line

Cell Membrane: ME, metabolism  
 Dihydropyridines: ME, metabolism  
 \*Dihydropyridines: PD, pharmacology  
 Drug Interactions  
 Ethosuximide: PD, pharmacology  
 Gallopamil: PD, pharmacology  
 Humans  
 Isradipine: ME, metabolism  
 Mibefradil: ME, metabolism  
 \*Mibefradil: PD, pharmacology  
 \*Myocardial Contraction: DE, drug effects  
 Perfusion  
 Radioligand Assay  
 Rats  
 Rats, Wistar  
 Research Support, Non-U.S. Gov't

\*Ventricular Pressure: DE, drug effects  
 RN 116644-53-2 (Mibefradil); 16662-47-8 (Gallopamil); 75695-93-1  
 (Isradipine); 77-67-8 (Ethosuximide); 88150-42-9 (Amlodipine)  
 CN 0 (Calcium Channel Blockers); 0 (Calcium Channels, L-Type); 0  
 (Dihydropyridines)

L103 ANSWER 133 OF 198 MEDLINE on STN  
 ACCESSION NUMBER: 2000107201 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 10640293  
 TITLE: Effects of the T-type **Ca(2+)** channel  
 blocker **mibefradil** on repolarization of guinea  
 pig, rabbit, dog, monkey, and human **cardiac**  
 tissue.  
 AUTHOR: Benardeau A; Weissenburger J; Hondeghem L; Ertel E A  
 CORPORATE SOURCE: F. Hoffmann-La Roche, Basel, Switzerland.  
 SOURCE: Journal of pharmacology and experimental therapeutics,  
 (2000 Feb) 292 (2) 561-75.  
 Journal code: 0376362. ISSN: 0022-3565.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200002  
 ENTRY DATE: Entered STN: 20000309  
 Last Updated on STN: 20000309  
 Entered Medline: 20000222

ED Entered STN: 20000309  
 Last Updated on STN: 20000309  
 Entered Medline: 20000222

AB At supratherapeutic doses (2- to 5-fold), the T-type **Ca(2+)** antagonist  
**mibefradil** modifies the T/U wave of the human ECG. In this study, we show  
 that this effect is observed in conscious monkeys and is duplicated by  
 verapamil or diltiazem. We then evaluate the proarrhythmic risk of such  
 alterations of **cardiac** repolarization by examining the actions  
 of **mibefradil** on **cardiac** action potentials (APs). In  
 isolated **cardiomyocytes** from guinea pigs or humans,  
**mibefradil** dose dependently shortens the plateau of the AP; this  
 effect is similar to other **Ca(2+)** antagonists and opposite to drugs having  
 class III antiarrhythmic properties. The metabolites of **mibefradil**,  
 singly or in combination, also shorten APs. In isolated rabbit  
**hearts**, **noncardiodepressant** concentrations of  
**mibefradil** have no effect on monophasic action potentials (MAPs),  
 whereas **cardiodepressant** levels produce a slight nonsignificant  
 lengthening. In **hearts** of open-chest bradycardic dogs,

**mibefradil** has no effect on MAP dispersion or on QT interval and shortens MAPs slightly; although high doses produce atrioventricular block, likely through  $\text{Ca}^{2+}$  antagonism, arrhythmias are never observed. In contrast, d-sotalol lengthens QT interval and MAPs, increases dispersion, and produces arrhythmias. Together, these in vitro and in vivo results suggest that **mibefradil** carries no **proarrhythmic** risk despite changes in T/U wave morphology. Although these changes resemble those observed with class III compounds, they also are seen with nonproarrhythmic compounds such as verapamil and diltiazem. In conclusion, the classical models used in the present study could not link the changes in T/U wave morphology produced by **mibefradil** and verapamil to any experimental marker of **proarrhythmic** liability.

CT Check Tags: Female; In Vitro; Male  
 \*Action Potentials: DE, drug effects  
 Animals  
 Anti-Arrhythmia Agents: PD, pharmacology  
   **Arrhythmia: CI, chemically induced**  
   **Calcium Channel Blockers: CL, classification**  
   **\*Calcium Channel Blockers: PD, pharmacology**  
 Diltiazem: PD, pharmacology  
 Dogs  
 Dose-Response Relationship, Drug  
 Drug Interactions  
 \*Electrocardiography: DE, drug effects  
 Guinea Pigs  
   **\*Heart: DE, drug effects**  
 Heart Atria: DE, drug effects  
 Humans  
 \*Mibefradil: PD, pharmacology  
 Rabbits  
 Saimiri  
 Sotalol: PD, pharmacology  
 Telemetry  
 Time Factors  
 Verapamil: PD, pharmacology  
 RN 116644-53-2 (Mibefradil); 3930-20-9 (Sotalol); 42399-41-7 (Diltiazem);  
 52-53-9 (Verapamil)  
 CN 0 (Anti-Arrhythmia Agents); 0 (Calcium Channel Blockers)

L103 ANSWER 134 OF 198 MEDLINE on STN  
 ACCESSION NUMBER: 2000143307 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 10681072  
 TITLE: Comparison of the efficacy and safety of losartan (50-100 mg) with the T-type **calcium channel** blocker **mibefradil** (50-100 mg) in mild to moderate **hypertension**.  
 AUTHOR: Chung O; Hinder M; Sharma A M; Bonner G; Middeke M; Platon J; Unger T  
 CORPORATE SOURCE: Institute of Pharmacology, Christian-Albrechts-University, Kiel, Germany.. oliver.chung@pharmakologie.uni-kiel.de  
 SOURCE: Fundamental & clinical pharmacology, (2000 Jan-Feb) 14 (1) 31-41.  
 Journal code: 8710411. ISSN: 0767-3981.  
 PUB. COUNTRY: France  
 DOCUMENT TYPE: (CLINICAL TRIAL)  
 Journal; Article; (JOURNAL ARTICLE)  
 (MULTICENTER STUDY)  
 (RANDOMIZED CONTROLLED TRIAL)  
 LANGUAGE: English

FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200003  
 ENTRY DATE: Entered STN: 20000330  
 Last Updated on STN: 20000330  
 Entered Medline: 20000320

ED Entered STN: 20000330

Last Updated on STN: 20000330

Entered Medline: 20000320

AB The objective of this study was to compare the **antihypertensive** efficacy and safety of losartan and **mibefradil**. 324 outpatients (57 +/- 9.2 years) with mild to moderate **hypertension** were randomly allocated in a double-blind fashion to receive 50 mg of losartan or mibefradil once daily p.o. for 6 weeks after 2 weeks of placebo run-in. Titration was then forced to 100 mg of losartan or mibefradil for an additional 6 weeks. Patients were assessed at baseline, 6 and 12 weeks. The primary efficacy variable was change in predose sitting diastolic (SDBP) and systolic (SSBP) blood pressure at 12 weeks. Secondary variables included change in mean 24-hour ambulatory blood pressure and comparison of safety and tolerability. Both treatments lowered SSBP and SDBP at 6 and 12 weeks (week 6: mibefradil -14/-9 mm Hg; losartan -12/-7 mm Hg) (P < 0.001). The primary objective, a difference between treatments in reduction of SSBP and SDBP at week 12 could be demonstrated (mibefradil -22/-16 mm Hg; losartan -16/-10 mm Hg) (P=0.003 and P=0.001, respectively). Twenty-four-hour SBP and 24-hour DBP were reduced (P<0.001) within each treatment group at weeks 6 and 12. The secondary objective, a difference between treatments in reduction of 24-hour blood pressure at week 12 could be demonstrated (P<0.001). Twenty-four-hour **heart** rate was lowered in the **mibefradil** group at weeks 6 and 12 (P < 0.001). Responder rates at 6 and 12 weeks were 56.2% and 78.5% for mibefradil versus 56.1% and 55.3% for losartan (P = 0.001). Both treatments were equally well tolerated. This study demonstrates that 50 mg losartan is comparably effective to 50 mg **mibefradil** in the treatment of mild to moderate **hypertension** with 100 mg **mibefradil** being more potent than losartan.

CT Check Tags: Comparative Study; Female; Male  
 Adolescent  
 Adult  
 Aged

**Antihypertensive Agents: AE, adverse effects**

**\*Antihypertensive Agents: TU, therapeutic use**

Blood Pressure: DE, drug effects

Blood Pressure: PH, physiology

Blood Pressure Monitoring, Ambulatory

Body Weight: PH, physiology

**Calcium Channel Blockers: AE, adverse effects**

**\*Calcium Channel Blockers: TU, therapeutic use**

**\*Calcium Channels, T-Type: DE, drug effects**

Double-Blind Method

Electrocardiography: DE, drug effects

Humans

**\*Hypertension: DT, drug therapy**

**Hypertension: PP, physiopathology**

Losartan: AE, adverse effects

**\*Losartan: TU, therapeutic use**

Mibefradil: AE, adverse effects

**\*Mibefradil: TU, therapeutic use**

Middle Aged

RN 114798-26-4 (Losartan); 116644-53-2 (Mibefradil)

CN 0 (Antihypertensive Agents); 0 (Calcium Channel Blockers); 0 (Calcium Channels, T-Type)

L103 ANSWER 135 OF 198 MEDLINE on STN  
ACCESSION NUMBER: 1999300814 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 10372226  
TITLE: **Mibefradil**, a T-type and L-type **calcium channel** blocker, limits infarct size through a glibenclamide-sensitive mechanism.  
AUTHOR: Mocanu M M; Gadgil S; Yellon D M; Baxter G F  
CORPORATE SOURCE: Hatter Institute for Cardiovascular Studies, University College Hospital and Medical School, London, UK.  
SOURCE: Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy, (1999 Apr) 13 (2) 115-22.  
Journal code: 8712220. ISSN: 0920-3206.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199908  
ENTRY DATE: Entered STN: 19990820  
Last Updated on STN: 20000303  
Entered Medline: 19990811

ED Entered STN: 19990820  
Last Updated on STN: 20000303  
Entered Medline: 19990811

AB **Mibefradil** is a novel **calcium channel** blocker with activity at both L-type and T-type calcium channels. There are data suggesting that this compound can protect the ischemic/reperfused myocardium in spite of the fact that there is a very low abundance of T-type calcium channels within ventricular tissue. The aims of this study were two-fold. First, we wished to study the protective effect of **mibefradil** on **ischemia**/reperfusion injury in the isolated rat **heart** using infarct size as the endpoint of injury. In this respect, we compared **mibefradil** with amlodipine, a well-known and potent L-type **calcium channel** blocker, and with ischemic preconditioning, an intervention known to reduce infarct size consistently. Secondly, we investigated the possible mechanisms through which protection was achieved. For this second purpose, we examined the effects on protection of glibenclamide (an ATP-dependent K<sup>+</sup> channel blocker) and chelerythrine (a protein kinase C inhibitor). Isolated rat hearts were perfused in the Langendorff mode at constant pressure. Control, **mibefradil**-treated (0.3 microM), **mibefradil** plus glibenclamide (50 microM), and **mibefradil** plus chelerythrine (10 microM) treated **hearts** underwent 35 minutes regional **ischemia** followed by 120 minutes reperfusion. At the end of the experiments, infarct size was determined with triphenyltetrazolium chloride and was expressed as a percentage of the ischemic risk zone (I/R%). A significant reduction in infarct size with **mibefradil** treatment was observed (I/R 11.1 +/- 2.1% vs. 35.5 +/- 3.1% in controls). This was comparable with the infarct reduction seen with two 5-minute cycles of ischemic preconditioning (17.7 +/- 2.5%). Amlodipine 0.1 microM, a concentration that caused equivalent coronary vasodilatation as that produced by **mibefradil** treatment, had no significant effect on infarct size (I/R 29.7 +/- 3.5%). The protective effect of **mibefradil** was not significantly modified by the presence of the PKC inhibitor chelerythrine 10 microM (I/R 19.1 +/- 4.9%) but was abolished when glibenclamide 50 microM was coadministered with **mibefradil** prior to **ischemia** (I/R 28.1 +/- 4.7%). Neither chelerythrine nor glibenclamide alone had any influence on infarct size. We conclude from these data that **mibefradil**, unlike amlodipine, markedly reduces



infarct size in the rat isolated heart. This protection is sensitive to inhibition by glibenclamide, suggesting that KATP channel opening may be an important additional and novel mechanism of mibefradil's action.

CT Check Tags: Comparative Study; In Vitro; Male Animals

\*Benzimidazoles: TU, therapeutic use

\*Calcium Channel Blockers: TU, therapeutic use

Disease Progression

Enzyme Activation

\*Glyburide: TU, therapeutic use

Hemodynamic Processes: DE, drug effects

Ischemic Preconditioning, Myocardial

Mibefradil

\*Myocardial Infarction: DT, drug therapy

Myocardial Infarction: PA, pathology

Protein Kinase C: DE, drug effects

Rats

Rats, Sprague-Dawley

Research Support, Non-U.S. Gov't

Risk Factors

\*Tetrahydronaphthalenes: TU, therapeutic use

RN 10238-21-8 (Glyburide); 116644-53-2 (Mibefradil)

CN 0 (Benzimidazoles); 0 (Calcium Channel Blockers); 0 (Tetrahydronaphthalenes); EC 2.7.1.37 (Protein Kinase C)

L103 ANSWER 136 OF 198 MEDLINE on STN

ACCESSION NUMBER: 97360918 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9217881

TITLE: Chronic T-type Ca<sup>2+</sup> channel blockade with **mibefradil** in hyperinsulinemic, insulin-resistant and **hypertensive** rats.

COMMENT: Erratum in: Cardiovasc Res 1998 Oct;40(1):230

AUTHOR: Verma S; Bhanot S; Hicke A; McNeill J H

CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, Canada.

SOURCE: Cardiovascular research, (1997 Apr) 34 (1) 121-8. Journal code: 0077427. ISSN: 0008-6363.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199708

ENTRY DATE: Entered STN: 19970825

Last Updated on STN: 20000303

Entered Medline: 19970811

ED Entered STN: 19970825

Last Updated on STN: 20000303

Entered Medline: 19970811

AB OBJECTIVES: To determine the effects of calcium antagonists on hyperinsulinemia, hypertriglyceridemia and hypertension, we examined the long-term effects of a new **calcium channel** blocker, **mibefradil**, on plasma insulin levels, plasma triglyceride levels and systolic blood pressure in insulin-resistant and hyperinsulinemic fructose-hypertensive (FH) rats. To this aim, both prevention and reversal protocols were employed. METHODS: Prevention study: Male Sprague-Dawley rats were procured at 6 weeks of age and were divided into: control (C, n = 6), control-treated (CT, n = 5), fructose (F, n = 7) and fructose-treated (FT, n = 6). Baseline measurements of plasma glucose, insulin and systolic blood pressure were conducted in all groups. At week

7, chronic mibefradil treatment (30 mg/kg/day, orally for 6 weeks) was initiated in the CT and FT groups. At week 8, the rats in the F and FT groups were started on a 66% fructose diet to induce hyperinsulinemia and hypertension. Weekly measurements of plasma insulin, plasma triglycerides and systolic blood pressure were conducted for the following 4 weeks. Reversal protocol: In a separate study, 8-week-treated FH rats and their age-matched controls were used to examine the effects of **mibefradil** on reversing fructose-induced hyperinsulinemia and **hypertension**. RESULTS: The F group exhibited hyperinsulinemia (3.2 +/- 0.1 vs. C 2.3 +/- 0.07 ng/ml, P < 0.05), hypertension (148 +/- 3 vs. C 121 +/- 1 mmHg, P < 0.002) and elevated triglyceride levels (5.4 +/- 0.8 vs. C 1.6 +/- 0.3 mM, P < 0.05). Chronic mibefradil treatment prevented the development of hyperinsulinemia (1.6 +/- 0.08 ng/ml, P < 0.004 vs. F) and hypertension (123 +/- 1 mmHg, P < 0.001 vs. F) and attenuated the development of hypertriglyceridemia. In the reversal study, mibefradil treatment reversed the development of hyperinsulinemia, hypertriglyceridemia and elevated BP in FH rats. Treatment did not affect the plasma glucose levels in any group (prevention or reversal). CONCLUSIONS: Long-term treatment with the calcium antagonist, **mibefradil**, both prevents and reverses the development of hyperinsulinemia, hypertriglyceridemia and **hypertension** in FH rats. These data indicate beneficial effects of mibefradil on carbohydrate and lipid metabolism in hyperinsulinemic and insulin-resistant states.

CT Check Tags: Male

Animals

\*Benzimidazoles: TU, therapeutic use

Blood Glucose: AN, analysis

\*Calcium Channel Blockers: TU, therapeutic use

Fructose

Hyperinsulinism: BL, blood

Hyperinsulinism: DT, drug therapy

\*Hyperinsulinism: PC, prevention & control

Hypertension: BL, blood

Hypertension: DT, drug therapy

\*Hypertension: PC, prevention & control

\*Insulin Resistance

Mibefradil

Rats

Rats, Sprague-Dawley

Research Support, Non-U.S. Gov't

\*Tetrahydronaphthalenes: TU, therapeutic use

Triglycerides: BL, blood

RN 116644-53-2 (Mibefradil); 30237-26-4 (Fructose)

CN 0 (Benzimidazoles); 0 (Blood Glucose); 0 (Calcium Channel Blockers); 0 (Tetrahydronaphthalenes); 0 (Triglycerides)

L103 ANSWER 137 OF 198 MEDLINE on STN

ACCESSION NUMBER: 97431348 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9286853

TITLE: Safety of **mibefradil**, a new once-a-day, selective T-type **calcium channel** antagonist.

AUTHOR: Kobrin I; Charlon V; Lindberg E; Pordy R

CORPORATE SOURCE: Hoffmann-LaRoche, Nutley, New Jersey 07710-1199, USA.

SOURCE: American journal of cardiology, (1997 Aug 21) 80 (4B) 40C-46C.

Journal code: 0207277. ISSN: 0002-9149.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)

(MULTICENTER STUDY)  
(RANDOMIZED CONTROLLED TRIAL)

LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 199709  
ENTRY DATE: Entered STN: 19970926  
Last Updated on STN: 20000303  
Entered Medline: 19970918

ED Entered STN: 19970926

Last Updated on STN: 20000303

Entered Medline: 19970918

AB The safety and tolerability of **mibefradil**, a selective T-type calcium channel antagonist, were evaluated in 3,430 patients with essential hypertension and chronic stable angina pectoris treated in 15 double-blind placebo and active-controlled clinical trials and 2 open-label, long-term safety studies. Of these patients, 2,636 were treated with the recommended doses of mibefradil (50 and 100 mg) and form the basis of this report. With the 50-mg dose of mibefradil, the incidence of each adverse event was similar to, or lower than, that observed in the placebo-treated patients. Treatment with the 100-mg dose was associated with a slightly higher incidence compared to placebo of dizziness (2.1% vs 1.8%), leg edema (3.5% vs 1.4%), fatigue (2.1% vs 1.4%), and lightheadedness (2.1% vs 0.4%). The incidence of headache (4.6%) and angina pectoris (1.1%) was more frequent in patients treated with placebo. In active-controlled trials, a lower incidence of pedal edema (5.1%) was observed with mibefradil compared to amlodipine (25.7%), diltiazem SR/CD (9.4%), or nifedipine SR/GITS (17.4%). Overall, mibefradil was better tolerated than amlodipine and nifedipine SR/GITS and was as well tolerated as diltiazem SR/CD. Rates of premature discontinuation due to clinically adverse experiences with the 50- and 100-mg doses were 2.5% and 3.5%, respectively, compared with placebo (3.5%). No consistent pattern of laboratory adverse experiences were observed for mibefradil. Sinus bradycardia (heart rate <45 beats/minute) and first-degree atrioventricular block were the only relevant treatment-emergent **electrocardiographic** changes that occurred more frequently with **mibefradil** than with placebo. No evidence of first-dose effects was observed in mibefradil-treated patients, and withdrawal effects were not observed in clinical trials. There were no clinically important differences in safety profiles in the demographic subgroups for age, gender, or race. The results of this comprehensive safety analysis indicate that treatment with the recommended doses of mibefradil is well tolerated and safe.

CT Check Tags: Comparative Study; Female; Male

Aged

Amlodipine: AD, administration & dosage

Amlodipine: AE, adverse effects

Angina Pectoris: DI, diagnosis

\*Angina Pectoris: DT, drug therapy

\*Benzimidazoles: AD, administration & dosage

Benzimidazoles: AE, adverse effects

\*Calcium Channel Blockers: AD, administration & dosage

Calcium Channel Blockers: AE, adverse effects

Chronic Disease

Drug Administration Schedule

Electrocardiography

Heart Conduction System: DE, drug effects

Heart Rate: DE, drug effects

Humans

\*Hypertension: DT, drug therapy

Mibefradil

Middle Aged  
Nifedipine: AD, administration & dosage  
Nifedipine: AE, adverse effects  
\*Tetrahydronaphthalenes: AD, administration & dosage  
Tetrahydronaphthalenes: AE, adverse effects  
RN 116644-53-2 (Mibefradil); 21829-25-4 (Nifedipine); 88150-42-9 (Amlodipine)  
CN 0 (Benzimidazoles); 0 (Calcium Channel Blockers); 0  
(Tetrahydronaphthalenes)

L103 ANSWER 138 OF 198 MEDLINE on STN  
ACCESSION NUMBER: 96248919 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 8667218  
TITLE: The effects of **mibefradil**, a novel  
**calcium channel** antagonist on ventricular  
**arrhythmias** induced by myocardial **ischemia**  
and programmed electrical stimulation.  
COMMENT: Erratum in: J Pharmacol Exp Ther 1996 Oct;279(1):442  
AUTHOR: Billman G E; Hamlin R L  
CORPORATE SOURCE: Department of Physiology, Ohio State University, Columbus,  
USA.  
SOURCE: Journal of pharmacology and experimental therapeutics,  
(1996 Jun) 277 (3) 1517-26.  
Journal code: 0376362. ISSN: 0022-3565.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199608  
ENTRY DATE: Entered STN: 19960819  
Last Updated on STN: 20000303  
Entered Medline: 19960806

ED Entered STN: 19960819  
Last Updated on STN: 20000303  
Entered Medline: 19960806

AB Calcium channel antagonists can reduce calcium overload induced by myocardial ischemia and thereby protect against malignant arrhythmias. However, these drugs may also adversely affect cardiac contractile function. **Mibefradil** is a new calcium antagonist that can inhibit **cardiac** calcium current without reducing myocardial force development. The effects of **mibefradil** on the inducibility of **arrhythmias** both before and during **ischemia** were therefore evaluated in animals with healed infarctions. First, a 2-min coronary occlusion was made during the last minute of exercise (n = 48): 25 animals had ventricular fibrillation (susceptible), whereas 23 did not (resistant). On a subsequent day, programmed electrical stimulation (PES, 8 paced beats followed by two extrastimuli) induced ventricular tachycardia in 19 of 25 susceptible animals but in none of the resistant animals (chi square = 24.6, P < .001). Verapamil (n = 14), diltiazem (n = 13) and mibefradil (n = 14) elicited significant dose-dependent decreases in refractory period and in the Q-Tc interval (except **mibefradil**) yet failed to prevent PES-induced **arrhythmias**. Diltiazem and verapamil also increased P-R interval and reduced the maximum rate of change of left ventricular pressure, whereas mibefradil did not. However, all three drugs abolished arrhythmias induced by PES during ischemia. In contrast, lidocaine suppressed PES-induced arrhythmias but failed to prevent ischemically induced arrhythmias. Thus **mibefradil** can prevent **ischemically** induced ventricular fibrillation without adverse actions on either A-V nodal conduction or contractile function. These data further suggest that calcium entry may play a critical role in the

initiation of ventricular fibrillation during ischemia, whereas other factors must be responsible for the extrasystoles induced by PES.

## CT Animals

\*Arrhythmia: DT, drug therapy

\*Benzimidazoles: PD, pharmacology

\*Calcium Channel Blockers: PD, pharmacology

Diltiazem: PD, pharmacology

Dogs

Dose-Response Relationship, Drug

Electric Stimulation

Electrocardiography: DE, drug effects

\*Heart Ventricles: DE, drug effects

Mibefradil

\*Myocardial Ischemia: DT, drug therapy

Research Support, Non-U.S. Gov't

\*Tetrahydronaphthalenes: PD, pharmacology

Verapamil: PD, pharmacology

RN 116644-53-2 (Mibefradil); 42399-41-7 (Diltiazem); 52-53-9 (Verapamil)

CN 0 (Benzimidazoles); 0 (Calcium Channel Blockers); 0 (Tetrahydronaphthalenes)

L103 ANSWER 139 OF 198 MEDLINE on STN

ACCESSION NUMBER: 97013103 MEDLINE

DOCUMENT NUMBER: PubMed ID: 8859939

TITLE: **Mibefradil, a selective calcium T-channel blocker, in stroke-prone spontaneously hypertensive rats.**

AUTHOR: Vacher E; Richer C; Fornes P; Clozel J P; Giudicelli

CORPORATE SOURCE: Departement de Pharmacologie, Faculte de Medecine Paris-Sud, Le Kremlin-Bicetre, France.

SOURCE: Journal of cardiovascular pharmacology, (1996 May) 27 (5) 686-94.

Journal code: 7902492. ISSN: 0160-2446.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199704

ENTRY DATE: Entered STN: 19970422

Last Updated on STN: 20000303

Entered Medline: 19970410

ED Entered STN: 19970422

Last Updated on STN: 20000303

Entered Medline: 19970410

AB Several types of antihypertensive agents, including calcium antagonists, have been reported to prevent stroke and prolong survival in stroke-prone spontaneously hypertensive rats (SHR-SP). We investigated whether mibefradil, a new calcium antagonist acting selectively at the level of T-type calcium channels, would be able to (a) limit or prevent the structural and functional alterations that develop in the cerebral arteries of SHR-SP before stroke and (b) suppress stroke and prolong survival. Mibefradil (30 mg/kg/day) was given orally to young salt-loaded SHR-SP from age 5 weeks to age 20 weeks. Blood pressure (BP) (in conscious animals), diuresis, and proteinuria were determined weekly. After 1012 weeks of treatment, middle cerebral arteries and aortas were removed from randomly selected control and treated SHR-SP. Aortic media thickness and collagen density were evaluated by histomorphometry. Middle cerebral arteries were mounted in a myograph for wall thickness determination and isometric tension recordings. Mibefradil completely prevented stroke and mortality, significantly limited the increase in BP,

and opposed the increases in diuresis and proteinuria observed in controls. Simultaneously, mibefradil abolished vascular fibrinoid necrosis formation in the brain and reduced arterial thickening in the cerebral artery as well as in the aorta. The maximal contractile responses of the cerebral arteries to potassium chloride and serotonin were greater in mibefradil-treated animals than in controls, as were the endothelium-dependent relaxant responses. Mibefradil, chronically administered to young SHRSP in a dose that limits the development of hypertension not only prevents stroke and mortality but also affords protection against the vascular structural alterations which develop with age in these animals and preserves or improves the cerebral artery's smooth muscle and endothelial cell functions.

CT Check Tags: In Vitro; Male  
Animals  
\*Benzimidazoles: TU, therapeutic use  
Blood Pressure: DE, drug effects  
Body Weight: DE, drug effects  
\*Calcium Channel Blockers: TU, therapeutic use  
Cerebral Arteries: DE, drug effects  
Cerebral Arteries: PH, physiology  
Cerebrovascular Disorders: PC, prevention & control  
Heart Rate: DE, drug effects  
\*Hypertension: DT, drug therapy  
Hypertension: PA, pathology  
Mibefradil  
Rats  
Rats, Inbred SHR  
\*Tetrahydronaphthalenes: TU, therapeutic use  
RN 116644-53-2 (Mibefradil)  
CN 0 (Benzimidazoles); 0 (Calcium Channel Blockers); 0 (Tetrahydronaphthalenes)

L103 ANSWER 140 OF 198 MEDLINE on STN  
ACCESSION NUMBER: 96390044 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 8797138  
TITLE: Effect of **calcium channel** blockade or angiotensin-converting enzyme inhibition on structure of coronary, renal, and other small arteries in spontaneously **hypertensive** rats.  
AUTHOR: Li J S; Schiffrin E L  
CORPORATE SOURCE: Multidisciplinary Research Group on Hypertension, Clinical Research Institute of Montreal, University of Montreal, Quebec, Canada.  
SOURCE: Journal of cardiovascular pharmacology, (1996 Jul) 28 (1) 68-74.  
Journal code: 7902492. ISSN: 0160-2446.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199701  
ENTRY DATE: Entered STN: 19970128  
Last Updated on STN: 20000303  
Entered Medline: 19970106  
ED Entered STN: 19970128  
Last Updated on STN: 20000303  
Entered Medline: 19970106  
AB Spontaneously hypertensive rats (SHRs) and Wistar-Kyoto control rats (WKY) were treated for 14 weeks with a novel **calcium channel** blocker, **mibefradil** (Ro40-5967), or an angiotensin-converting

enzyme inhibitor, cilazapril. Blood pressure was significantly reduced by treatment in SHR from > 200 mm Hg to 155 +/- 2 mm Hg by mibefradil and to 138 +/- 1 mm Hg by cilazapril (p < 0.01). Cardiac hypertrophy was significantly reduced by treatment but to a greater degree with cilazapril than with mibefradil. Conduit and large arteries also had significant regression of hypertrophy. Small arteries (luminal diameter, 200-300 microns) of the coronary, renal, mesenteric, and femoral circulations exhibited significant hypertrophy and remodeling in SHR in comparison to WKYs. Cilazapril treatment resulted in increased lumen, reduced media thickness, and media-to-lumen ratio in all four vascular beds. Mibefradil treatment induced regression of luminal diameter to a significant degree only in the mesenteric and femoral small arteries but decreased media thickness and media to lumen diameter in all four vascular beds. The greater extent of regression of **cardiac** and vascular hypertrophy and remodeling with cilazapril than with **mibefradil** may relate to the degree of blood pressure reduction, which, with the doses used, was larger with the angiotensin-converting enzyme inhibitor than with the calcium channel blocker. In WKY rats, treatment had no effect except with cilazapril on lumen diameter of small arteries and with **mibefradil** on **heart** weight, both of which increased. These results demonstrate the blood-pressure dependence of regression of cardiovascular hypertrophy and remodeling and the possibility of achieving "reverse remodeling" of large and small arteries with converting enzyme inhibition or calcium channel blockade in SHR, as well as the near absence of effects of these agents on cardiovascular characteristics in WKYs.

CT Check Tags: Comparative Study

\*Angiotensin-Converting Enzyme Inhibitors: PD, pharmacology

Animals

\*Benzimidazoles: PD, pharmacology

Blood Pressure: DE, drug effects

\*Calcium Channel Blockers: PD, pharmacology

\*Cilazapril: PD, pharmacology

\*Coronary Vessels: DE, drug effects

Coronary Vessels: PA, pathology

Femoral Artery: DE, drug effects

Femoral Artery: PA, pathology

Heart: DE, drug effects

Hypertension: DT, drug therapy

Mesenteric Arteries: DE, drug effects

Mesenteric Arteries: PA, pathology

Mibefradil

\*Microcirculation: DE, drug effects

Microcirculation: PA, pathology

Rats

Rats, Inbred SHR

Rats, Inbred WKY

\*Renal Artery: DE, drug effects

Renal Artery: PA, pathology

Renin: BL, blood

Research Support, Non-U.S. Gov't

\*Tetrahydronaphthalenes: PD, pharmacology

RN 116644-53-2 (Mibefradil); 92077-78-6 (Cilazapril)

CN 0 (Angiotensin-Converting Enzyme Inhibitors); 0 (Benzimidazoles); 0 (Calcium Channel Blockers); 0 (Tetrahydronaphthalenes); EC 3.4.23.15 (Renin)

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ACCESSION NUMBER: 2002:10991 BIOSIS

DOCUMENT NUMBER: PREV200200010991

TITLE: Low threshold T-type **calcium** current in rat embryonic chromaffin cells.

AUTHOR(S): Bournaud, R.; Hidalgo, J.; Yu, H.; Jaimovich, E.; Shimahara, T. [Reprint author]

CORPORATE SOURCE: Laboratoire de Neurobiologie Cellulaire et Moleculaire, CNRS, 91198, Gif-sur-Yvette, France  
shima@nbcn.cnrs-gif.fr

SOURCE: Journal of Physiology (Cambridge), (November 15th, 2001)  
Vol. 537, No. 1, pp. 35-44. print.  
CODEN: JPHYA7. ISSN: 0022-3751.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 28 Dec 2001  
Last Updated on STN: 25 Feb 2002

ED Entered STN: 28 Dec 2001

Last Updated on STN: 25 Feb 2002

AB 1. The gating kinetics and functions of low threshold T-type current in cultured chromaffin cells from rats of 19-20 days gestation (E19-E20) were studied using the patch clamp technique. Exocytosis induced by calcium currents was monitored by the measurement of membrane capacitance and amperometry with a carbon fibre sensor. 2. In cells cultured for 1-4 days, the embryonic chromaffin cells were immunohistochemically identified by using polyclonal antibodies against dopamine beta-hydroxylase (DBH) and syntaxin. The immuno-positive cells could be separated into three types, based on the recorded calcium current properties. Type I cells showed exclusively large low threshold T-type current, Type II cells showed only high voltage activated (HVA) calcium channel current and Type III cells showed both T-type and HVA currents. These cells represented 44%, 46% and 10% of the total, respectively. 3. T-type current recorded in Type I cells became detectable at -50 mV, reached its maximum amplitude of  $6.8 \pm 1.2$  pA pF<sup>-1</sup> (n = 5) at -10 mV and reversed around +50 mV. The current was characterized by criss-crossing kinetics within the -50 to -30 mV voltage range and a slow deactivation (deactivation time constant,  $\tau_{\text{d}} = 2$  ms at -80 mV). The channel closing and inactivation process included both voltage-dependent and voltage-independent steps. The **antihypertensive drug mibefradil** (200 nM) reduced the current amplitude to about 65% of control values. Ni<sup>2+</sup> also blocked the current in a dose-dependent manner with an IC<sub>50</sub> of 25  $\mu$ M. 4. T-type current in Type I cells did not induce exocytosis, while catecholamine secretion by exocytosis could be induced by HVA calcium current in both Type II and Type III cells. The failure to induce exocytosis by T-type current in Type I cells was not due to insufficient Ca<sup>2+</sup> influx through the T-type calcium channel. 5. We suggest that T-type current is expressed in developing immature chromaffin cells. The T-type current is replaced progressively by HVA calcium current during pre- and post-natal development accompanying the functional maturation of the exocytosis mechanism.

CC Cytology - Animal 02506

Biochemistry studies - General 10060

Enzymes - General and comparative studies: coenzymes 10802

Pathology - Therapy 12512

Endocrine - General 17002

Pharmacology - Cardiovascular system 22010

Development and Embryology - General and descriptive 25502

IT Major Concepts

Biochemistry and Molecular Biophysics; Endocrine System (Chemical Coordination and Homeostasis)

IT Parts, Structures, & Systems of Organisms

chromaffin cells: endocrine system

IT Chemicals & Biochemicals



dopamine beta-hydroxylase; high voltage activated **calcium** current; low threshold T-type **calcium** current: gating kinetics; **mibefradil: antihypertensive-drug, calcium channel blocker-drug, cardiovascular-drug**; nickel(II) ion; syntaxin

IT Miscellaneous Descriptors  
exocytosis

ORGN Classifier  
Muridae 86375  
Super Taxa  
Rodentia; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
rat: animal model, embryo  
Taxa Notes  
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 9013-38-1 (dopamine beta-hydroxylase)  
116644-53-2 (mibefradil)  
14701-22-5 (nickel(II) ion)

L103 ANSWER 142 OF 198 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2000:530593 BIOSIS  
DOCUMENT NUMBER: PREV2000000530593  
TITLE: Acute renal and **cardiovascular** hemodynamics of **Mibefradil** in conscious SHR.  
AUTHOR(S): Chung, O. [Reprint author]; Kuehl, H. [Reprint author]; Unger, Th. [Reprint author]  
CORPORATE SOURCE: Institute of Pharmacology, Univ. Kiel, Kiel, Germany  
SOURCE: Hypertension (Baltimore), (October, 2000) Vol. 36, No. 4, pp. 671. print.  
Meeting Info.: 5th Annual Meeting of the European Council for Blood Pressure and Cardiovascular Research. Noordwijkerhout, Netherlands. October 13-15, 2000. CODEN: HPRTDN. ISSN: 0194-911X.  
DOCUMENT TYPE: Conference; (Meeting)  
Conference; (Meeting Poster)  
LANGUAGE: English  
ENTRY DATE: Entered STN: 6 Dec 2000  
Last Updated on STN: 11 Jan 2002

ED Entered STN: 6 Dec 2000  
Last Updated on STN: 11 Jan 2002

CC Biochemistry studies - General 10060  
General biology - Symposia, transactions and proceedings 00520  
Biochemistry studies - Minerals 10069  
Pathology - Therapy 12512  
**Cardiovascular system - Physiology and biochemistry 14504**  
**Cardiovascular system - Heart pathology 14506**  
Urinary system - Physiology and biochemistry 15504  
Pharmacology - General 22002  
Pharmacology - Cardiovascular system 22010

IT Major Concepts  
Urinary System (Chemical Coordination and Homeostasis); Pharmacology;  
**Cardiovascular System (Transport and Circulation)**

IT Parts, Structures, & Systems of Organisms  
kidney: excretory system, renal artery

IT Diseases  
reflex tachycardia: **heart disease**

IT Chemicals & Biochemicals  
**amlodipine: antihypertensive-drug, calcium channel blocker-drug, comparison; calcium (II) ion; calcium (II) ion**

channel: T-type, pharmacologic blockade; mibefradil [Mib]:  
 antianginal-drug, antihypertensive-drug, calcium channel blocker-drug,  
 acute effects, comparison, dose, intravenous administration;  
 nifedipine: antihypertensive-drug, calcium channel blocker-drug,  
 comparison; verapamil: antihypertensive-drug, calcium channel  
 blocker-drug, comparison

## IT Miscellaneous Descriptors

acute **cardiovascular** hemodynamics; acute renal hemodynamics;  
**heart** rate: measurement; mean arterial blood pressure:  
 measurement; renal blood flow: measurement; renal function; renal  
 resistance: measurement; Meeting Poster

## ORGN Classifier

Muridae 86375

## Super Taxa

Rodentia; Mammalia; Vertebrata; Chordata; Animalia

## Organism Name

rat: animal model, conscious, **hypertensive**, male

## Taxa Notes

Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,  
 Rodents, Vertebrates

## RN 88150-42-9 (amlodipine)

14127-61-8 (**calcium** (II) ion)

116644-53-2 (mibefradil)

116644-53-2 (Mib)

21829-25-4 (nifedipine)

52-53-9 (verapamil)

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 STN

ACCESSION NUMBER: 2001:56527 BIOSIS

DOCUMENT NUMBER: PREV200100056527

TITLE: Acute renal hemodynamics and **cardiovascular**  
 effects of **mibefradil** in conscious spontaneously  
**hypertensive** rats.

AUTHOR(S): Chung, O. [Reprint author]; Kuehl, H. [Reprint author];  
 Unger, T. [Reprint author]

CORPORATE SOURCE: Institute of Pharmacology, University Kiel, Kiel, Germany  
 SOURCE: Journal of Hypertension, (2000) Vol. 18, No. Suppl. 4, pp.  
 S249. print.

Meeting Info.: 18th Scientific Meeting of the International  
 Society of Hypertension. Chicago, Illinois, USA. August  
 20-24, 2000. International Society of Hypertension.  
 CODEN: JOHYD3. ISSN: 0263-6352.

DOCUMENT TYPE: Conference; (Meeting)  
 Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 24 Jan 2001

Last Updated on STN: 12 Feb 2002

ED Entered STN: 24 Jan 2001

Last Updated on STN: 12 Feb 2002

CC Pharmacology - Cardiovascular system 22010

General biology - Symposia, transactions and proceedings 00520

Biochemistry studies - General 10060

Pathology - Therapy 12512

**Cardiovascular system - Physiology and biochemistry 14504**

**Cardiovascular system - Blood vessel pathology 14508**

Pharmacology - General 22002

Pharmacology - Urinary system 22032

Allergy 35500

IT Major Concepts

Pharmacology; Cardiovascular System (Transport and Circulation)

IT Diseases  
     hypertension: vascular disease, drug treatment, impaired renal function  
     Hypertension (MeSH)

IT Chemicals & Biochemicals  
     amlodipine: antihypertensive-drug, renal-acting-drug, L-type calcium channel blocker, acute renal dynamic effects, cardiovascular effects, comparative study; mibefradil: antihypertensive-drug, renal-acting-drug, T-type calcium channel blocker, acute renal dynamic effects, cardiovascular effects, comparative study; nifedipine: antihypertensive-drug, renal-acting-drug, L-type calcium channel blocker, acute renal dynamic effects, cardiovascular effects, comparative study; verapamil: antihypertensive-drug, renal-acting-drug, L-type calcium channel blocker, acute renal dynamic effects, cardiovascular effects, comparative study

IT Miscellaneous Descriptors  
     Meeting Abstract

ORGN Classifier  
     Muridae 86375  
     Super Taxa  
     Rodentia; Mammalia; Vertebrata; Chordata; Animalia  
     Organism Name  
     SHR rat: conscious animal model  
     Taxa Notes  
     Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 88150-42-9 (amlodipine)  
     116644-53-2 (mibefradil)  
     21829-25-4 (nifedipine)  
     52-53-9 (verapamil)

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ACCESSION NUMBER: 2000:320475 BIOSIS  
 DOCUMENT NUMBER: PREV200000320475  
 TITLE: Effects of calcium channel blockers on cloned cardiac K<sup>+</sup> channels IKr and IKs.  
 AUTHOR(S): Chouabe, C.; Drici, M.-D.; Romey, G.; Barhanin, J. [Reprint author]  
 CORPORATE SOURCE: Institut de Pharmacologie Moleculaire et Cellulaire-CNRS, 660 Route des Lucioles, Sophia Antipolis, F-06560, Valbonne, France  
 SOURCE: Therapie (London), (Janvier-Fevrier, 2000) Vol. 55, No. 1, pp. 195-202. print.  
           CODEN: THERAP. ISSN: 0040-5957.  
 DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 26 Jul 2000  
           Last Updated on STN: 7 Jan 2002

ED Entered STN: 26 Jul 2000

Last Updated on STN: 7 Jan 2002

AB Cloned HERG and KvLQT1-IsK K<sup>+</sup> channels have been expressed in mammalian cells and assayed as a target for calcium channel blockers. These channels generate the rapid and slow components of the cardiac delayed rectifier K<sup>+</sup> current, and mutations can affect them that lead to long QT syndromes. HERG is blocked by bepridil (EC<sub>50</sub>=0.55 μM), verapamil (EC<sub>50</sub>=0.83 μM) and mibefradil (EC<sub>50</sub>=1.43 μM), whereas nitrendipine and diltiazem have negligible effects. Steady-state activation and inactivation parameters are shifted to more negative values in the

presence of the blockers. Similarly, KvLQT1-IsK is inhibited by bepridil (EC50= 10.0  $\mu$ M) and mibefradil (EC50=11.8  $\mu$ M), whilst being insensitive to nitrendipine, diltiazem or verapamil. This work may help to understand the mechanisms of action of verapamil in certain ventricular tachycardias as well as some of the deleterious adverse **cardiac** events associated with bepridil and **mibefradil**.

CC Cytology - Animal 02506  
     **Cardiovascular system - Physiology and biochemistry 14504**  
     **Cardiovascular system - Heart pathology 14506**  
     Pharmacology - Cardiovascular system 22010  
 IT Major Concepts  
     Pharmacology; **Cardiovascular System (Transport and Circulation)**  
 IT Parts, Structures, & Systems of Organisms  
     **cardiac potassium channels**  
 IT Diseases  
     **arrhythmia: heart disease**  
     **Arrhythmia (MeSH)**  
 IT Diseases  
     long QT syndrome: **heart disease**  
     Long QT Syndrome (MeSH)  
 IT Diseases  
     torsade de pointes: **heart disease**  
     Torsades de Pointes (MeSH)  
 IT Chemicals & Biochemicals  
     **bepridil: calcium channel blocker-drug; calcium channel**  
     **blockers; diltiazem: calcium channel blocker-drug;**  
     **mibefradil: calcium channel blocker-drug; nitrendipine:**  
     **calcium channel blocker-drug; verapamil: calcium channel**  
     **blocker-drug**  
 ORGN Classifier  
     Cercopithecidae 86205  
     Super Taxa  
     Primates; Mammalia; Vertebrata; Chordata; Animalia  
     Organism Name  
     COS-7 cell line  
     Taxa Notes  
     Animals, Chordates, Mammals, Nonhuman Mammals, Nonhuman Vertebrates,  
     Nonhuman Primates, Primates, Vertebrates  
 RN 64706-54-3 (bepridil)  
     42399-41-7 (diltiazem)  
     116644-53-2 (mibefradil)  
     39562-70-4 (nitrendipine)  
     52-53-9 (verapamil)

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ACCESSION NUMBER: 2000:461594 BIOSIS  
 DOCUMENT NUMBER: PREV200000461594  
 TITLE: Comparison of effects of nitrendipine, lacidipine and  
     **mibefradil** on postischaemic myocardial damage in  
     isolated rat **hearts**.  
 AUTHOR(S): Arh, Maj [Reprint author]; Budihna, Metka V. [Reprint  
     author]  
 CORPORATE SOURCE: Department of Pharmacology and Experimental Toxicology,  
     Faculty of Medicine, Korytkova 2, 1000, Ljubljana, Slovenia  
 SOURCE: Pfluegers Archiv European Journal of Physiology, (2000)  
     Vol. 440, No. 5 Supplement, pp. R149-R150. print.  
     CODEN: PFLABK. ISSN: 0031-6768.  
 DOCUMENT TYPE: Article  
 LANGUAGE: English

ENTRY DATE: Entered STN: 25 Oct 2000  
Last Updated on STN: 10 Jan 2002

ED Entered STN: 25 Oct 2000  
Last Updated on STN: 10 Jan 2002

AB During ischaemia and reperfusion increased cytosolic Ca<sup>2+</sup> is one of the important causes for ischaemic-reperfusion myocardial injury. In the present study we compared effects of preferentially L-type Ca<sup>2+</sup> antagonists nitrendipine (NT) and lacidipine (LP), and of mibefradil (MB) a Ca<sup>2+</sup> antagonist with higher affinity to T- than to L-type channels on myocardial function during reperfusion. Coronary flow (CF), heart rate (HR), left ventricular pressure (LVP), lactate dehydrogenase (LDH) release rate and ECG were registered during 40 min of reperfusion following 30 min of global zero flow ischaemia in Langendorff's isolated rat hearts. Either NT (100 nmol/L) or LP (10 nmol/L) or MB (100 nmol/L) was added to Krebs-Henseleit solution 10 min before ischaemia till the end of experiments. All three drugs influenced CF, HR and LVP. All of them decreased LDH release rate ( $P < 0.05$ , in  $\mu\text{kat/g.min}$ ) when compared with control hearts ( $53.2 \pm 5.1$ ): MB ( $19.4 \pm 4.3$ ) > LP ( $30.7 \pm 6.6$ ) > NT ( $43.3 \pm 2.8$ ). NT reduced the duration of continuous arrhythmias at the beginning of reperfusion (to  $59.1 \pm 6.1$  % of ischaemic controls) as well as the number of single arrhythmic events arising during the whole period of reperfusion (to  $26.1 \pm 6.0$  % of ischaemic controls). MB diminished only single arrhythmic events during reperfusion to  $39.1 \pm 17.3$  % of ischaemic controls. LP did not affect the onset of arrhythmias. Results of our experiments indicate a relatively greater importance of T-type than of L-type Ca<sup>2+</sup> channels in the arising of postischaemic myocardial damage.

CC **Cardiovascular system - Heart pathology 14506**  
Biochemistry studies - General 10060  
Enzymes - General and comparative studies: coenzymes 10802  
Pathology - Therapy 12512  
    **Cardiovascular system - Physiology and biochemistry 14504**  
    **Cardiovascular system - Blood vessel pathology 14508**  
Pharmacology - General 22002  
Pharmacology - Cardiovascular system 22010

IT Major Concepts  
    Pharmacology; Cardiovascular System (Transport and Circulation)

IT Parts, Structures, & Systems of Organisms  
    **heart: circulatory system, postischemic myocardial damage**

IT Diseases  
    **arrhythmia: heart disease**  
    **Arrhythmia (MeSH)**

IT Diseases  
    **ischemic-reperfusion myocardial injury: vascular disease**

IT Chemicals & Biochemicals  
    **lacidipine: calcium channel blocker-drug, calcium antagonist, effect; lactate dehydrogenase: release rate; mibefradil: calcium channel blocker-drug, calcium antagonist, effect; nitrendipine: calcium channel blocker-drug, calcium antagonist, effect**

IT Miscellaneous Descriptors  
    coronary flow; heart rate; left ventricular pressure

ORGN Classifier  
    Muridae 86375  
Super Taxa  
    Rodentia; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
    rat: strain-Wistar  
Taxa Notes  
    Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 103890-78-4 (lacidipine)  
 9001-60-9 (lactate dehydrogenase)  
 116644-53-2 (mibefradil)  
 39562-70-4 (nitrendipine)

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ACCESSION NUMBER: 2000:41011 BIOSIS

DOCUMENT NUMBER: PREV200000041011

TITLE: The T-type  $\text{Ca}^{2+}$  channel blocker mibefradil prevents the development of a substrate for atrial fibrillation by tachycardia-induced atrial remodeling in dogs.

AUTHOR(S): Fareh, Samir; Benardeau, Agnes; Thibault, Bernard; Nattel, Stanley [Reprint author]

CORPORATE SOURCE: Research Center, Montreal Heart Institute, 5000 Belanger St E, Montreal, PQ, H1T 1C8, Canada

SOURCE: Circulation, (Nov. 23, 1999) Vol. 100, No. 21, pp. 2191-2197. print.

CODEN: CIRCAZ. ISSN: 0009-7322.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 19 Jan 2000

Last Updated on STN: 31 Dec 2001

ED Entered STN: 19 Jan 2000

Last Updated on STN: 31 Dec 2001

AB Background:  $\text{Ca}^{2+}$  overload is believed to play a role in tachycardia-induced atrial electrophysiological remodeling. L-type  $\text{Ca}^{2+}$  channel blockers attenuate effective refractory period (ERP) changes caused by 24 hours of atrial tachycardia but may not substantially alter atrial fibrillation (AF) inducibility. This study assessed the effects of the T-type  $\text{Ca}^{2+}$  channel blocker mibefradil on tachycardia-induced atrial remodeling. Methods and Results: Dogs subjected to rapid atrial pacing (400 bpm) for 7 days were treated with mibefradil (100 mg/d, n=8) or matching placebo (n=10) in blinded fashion. Radiofrequency ablation of atrioventricular conduction and ventricular pacing were used to control ventricular rate. Placebo dogs showed significant decreases in atrial ERP (76+-5 ms at a cycle length of 300 ms) and increases in ERP heterogeneity (27.7+-2.4%), AF duration (414+-232 seconds), and AF inducibility by single extrastimuli (41+-10% of sites) compared with 10 unpaced control dogs (ERP 114+-3 ms, ERP heterogeneity 13.8+-0.9%, AF duration 7+-3 seconds, AF inducibility 1.9+-1.0% of sites). The changes caused by atrial tachycardia were strongly attenuated in mibefradil dogs, with ERPs averaging 102+-7 ms, ERP heterogeneity 18.8+-1.4%, AF duration 3+-1 seconds, and AF inducibility 9.6+-4.0% of sites. Among mibefradil-treated dogs, ERP, AF duration, and inducibility correlated with plasma drug concentration. Acute mibefradil administration did not alter ERP or AF. Conclusions: Mibefradil, a drug with strong T-type  $\text{Ca}^{2+}$  channel blocking properties, prevents AF-promoting electrophysiological remodeling by atrial tachycardia. These findings have important potential implications for the mechanisms of tachycardia-induced atrial remodeling and demonstrate the feasibility of preventing electrical remodeling caused by several days of atrial tachycardia.

CC Pharmacology - General 22002

Pathology - Therapy 12512

**Cardiovascular system - General and methods 14501**

IT Major Concepts

Pharmacology; **Cardiovascular System (Transport and Circulation)**

IT Parts, Structures, & Systems of Organisms

atrium: circulatory system, tachycardia-induced remodelling

IT Diseases  
     atrial fibrillation: **heart** disease, duration, inducibility,  
     prevention, substrate development  
     Atrial Fibrillation (MeSH)

IT Chemicals & Biochemicals  
     **mibefradil: antiarrhythmic-drug, T-type calcium channel blocker**

IT Miscellaneous Descriptors  
     **calcium overload; effective refractory period: heterogeneity**

ORGN Classifier  
     Canidae 85765  
     Super Taxa  
     Carnivora; Mammalia; Vertebrata; Chordata; Animalia  
     Organism Name  
     dog: animal model  
     Taxa Notes  
     Animals, Carnivores, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman  
     Mammals, Vertebrates

RN 116644-53-2 (mibefradil)

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ACCESSION NUMBER: 1999:216501 BIOSIS  
 DOCUMENT NUMBER: PREV199900216501  
 TITLE: Cytosolic **calcium** and lymphoproliferative  
     response during **calcium** antagonism in men.  
 AUTHOR(S): Lijnen, P. [Reprint author]; Fagard, R.; Petrov, V.  
 CORPORATE SOURCE: Hypertension Unit, Herestraat 49, Campus Gasthuisberg,  
     B-3000, Leuven, Belgium  
 SOURCE: European Journal of Clinical Pharmacology, (Feb., 1999)  
     Vol. 54, No. 12, pp. 911-915. print.  
     CODEN: EJCPAS. ISSN: 0031-6970.  
 DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 26 May 1999  
     Last Updated on STN: 26 May 1999

ED Entered STN: 26 May 1999

Last Updated on STN: 26 May 1999

AB Objective: A double-blind, placebo-controlled parallel study was conducted  
 on the effect of mibefradil, both an L- and T-type Ca<sup>2+</sup>-channel blocker  
 with a more selective blockade of T-type channels, administered once daily  
 for 1 week to normal male subjects, on blood pressure, intracellular  
 cationic concentrations, sodium-proton exchange rate and 3H-thymidine  
 incorporation in peripheral blood mononuclear cells (PBMC). Methods:  
 After a 1-week run-in period on placebo, the subjects (n = 40) were  
 allocated to a placebo or a mibefradil group. Placebo or 50 mg mibefradil  
 was administered once daily in the morning for 1 week. All subjects were  
 investigated at baseline and after 1 week of placebo or mibefradil  
 administration. Standing or recumbent blood pressure and **heart**  
 rate of subjects in the **mibefradil** group was decreased (P < 0.05  
 or less) compared with that of subjects in the placebo group. Results:  
 Decreased (P < 0.001) intracellular free Ca<sup>2+</sup> concentration and reduced (P  
 < 0.001) 3H-thymidine incorporation in the PBMC were observed in the  
 mibefradil-treated subjects. The intracellular sodium, potassium or  
 magnesium concentration as well as the sodium-proton exchange rate were  
 not changed during mibefradil administration. Conclusion: The blood  
 pressure lowering action of mibefradil in men is accompanied by a decrease  
 in intracellular free Ca<sup>2+</sup> concentration. Mibefradil also reduced the  
 3H-thymidine incorporation or de novo DNA synthesis in PBMC by modulating  
 the calcium homeostasis.

CC Cardiovascular system - General and methods 14501

Biochemistry studies - General 10060  
 Pharmacology - General 22002  
 Metabolism - General metabolism and metabolic pathways 13002

IT Major Concepts  
     **Cardiovascular System (Transport and Circulation);**  
     Pharmacology

IT Parts, Structures, & Systems of Organisms  
     peripheral blood mononuclear cell: blood and lymphatics, immune system

IT Chemicals & Biochemicals  
     **calcium: homeostasis; magnesium; mibefradil:**  
     **antihypertensive-drug, calcium channel blocker-drug; potassium;**  
     sodium

IT Miscellaneous Descriptors  
     blood pressure; **heart** rate; sodium-proton exchange rate

ORGN Classifier  
     Hominidae 86215  
     Super Taxa  
     Primates; Mammalia; Vertebrata; Chordata; Animalia  
     Organism Name  
     human: male  
     Taxa Notes  
     Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 7440-70-2 (**calcium**)  
 7439-95-4 (magnesium)  
 116644-53-2 (mibefradil)  
 7440-09-7 (potassium)  
 7440-23-5 (sodium)

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ACCESSION NUMBER: 1999:539016 BIOSIS  
 DOCUMENT NUMBER: PREV199900539016  
 TITLE: **Calcium channel** blockade (CCB) with  
     **mibefradil** (Mib) reduces proteinuria and glomerular  
     sclerosis, preserves GFR and normalizes glomerular blood  
     pressure (PGC) in DOCA/salt (DS) **hypertensive**  
     rats.

AUTHOR(S): Baylis, C. [Reprint author]; Qiu, C.; Engels, K. [Reprint  
 author]

CORPORATE SOURCE: Physiology, WVU, Morgantown, WV, USA  
 SOURCE: Journal of the American Society of Nephrology, (Sept.,  
 1999) Vol. 10, No. PROGRAM AND ABSTR. ISSUE, pp. 654A-655A.  
 print.  
 Meeting Info.: 32nd Annual Meeting of the American Society  
 of Nephrology. Miami Beach, Florida, USA. November 1-8,  
 1999. American Society of Nephrology.  
 CODEN: JASNEU. ISSN: 1046-6673.

DOCUMENT TYPE: Conference; (Meeting)  
 Conference; Abstract; (Meeting Abstract)  
 Conference; (Meeting Poster)

LANGUAGE: English

ENTRY DATE: Entered STN: 10 Dec 1999  
 Last Updated on STN: 10 Dec 1999

ED Entered STN: 10 Dec 1999  
 Last Updated on STN: 10 Dec 1999

CC Pharmacology - Drug metabolism and metabolic stimulators 22003  
 Biophysics - Membrane phenomena 10508  
 Metabolism - Minerals 13010  
     **Cardiovascular system - Physiology and biochemistry 14504**  
 Urinary system - Pathology 15506



Urinary system - Physiology and biochemistry 15504  
**Cardiovascular system - Blood vessel pathology 14508**  
 General biology - Symposia, transactions and proceedings 00520  
 Toxicology - Pharmacology 22504  
 Pharmacology - Endocrine system 22016  
 Laboratory animals - General 28002  
 Endocrine - Adrenals 17004  
 Biochemistry studies - General 10060  
 Nutrition - Pathogenic diets 13216  
 Nutrition - Minerals 13206  
 Biochemistry studies - Sterols and steroids 10067  
 Biochemistry studies - Minerals 10069

IT Major Concepts

**Cardiovascular System (Transport and Circulation);**

Pharmacology; Urinary System (Chemical Coordination and Homeostasis)

IT Chemicals & Biochemicals

**mibefradil: antihypertensive-drug, renal-acting-drug, calcium  
 channel blocker, proteinuria reduction, glomerular blood pressure  
 normalization, glomerulosclerosis reduction**

IT Miscellaneous Descriptors

Meeting Abstract; Meeting Poster

ORGN Classifier

Muridae 86375

Super Taxa

Rodentia; Mammalia; Vertebrata; Chordata; Animalia

Organism Name

deoxycorticosterone acetate-salt **hypertensive** rat: animal  
 model

Taxa Notes

Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,  
 Rodents, Vertebrates

RN 116644-53-2 (mibefradil)

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ACCESSION NUMBER: 1999:229460 BIOSIS

DOCUMENT NUMBER: PREV199900229460

TITLE: The effects of mibefradil and enalapril on 24-hour blood  
 pressure control and left ventricular mass in patients with  
 mild to moderate **hypertension**: Double-blind,  
 randomized trial.

AUTHOR(S): Martina, Benedict [Reprint author]; Lorz, Werner; Frach,  
 Beate; Bart, Thomas; Battegay, Edouard J.

CORPORATE SOURCE: Medical University Outpatient Clinic, University Hospital,  
 Petersgraben 4, CH-4031, Basel, Switzerland

SOURCE: Journal of Cardiovascular Pharmacology, (April, 1999) Vol.  
 33, No. 4, pp. 647-651. print.  
 CODEN: JCPCDT. ISSN: 0160-2446.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 17 Jun 1999

Last Updated on STN: 17 Jun 1999

ED Entered STN: 17 Jun 1999

Last Updated on STN: 17 Jun 1999

AB In this prospective, double-blind, monocenter drug trial, 48 primary care  
 patients with mild to moderate essential **hypertension** were  
 randomized to **mibefradil**, 50 mg, titrated to 100 mg, or  
 enalapril, 20 mg, titrated to 2 X 20 mg. Ambulatory 24-h blood pressure  
 measurements (ABPM) and echocardiography were performed at baseline and  
 after 12 weeks' treatment. Complete data from 43 patients were analyzed.

Mibefradil (n 22; titration, 13 patients) reduced mean 24-h ABP from 159 +/- 14/102 +/- 7 mm Hg to 140 +/- 10/89 +/- 7 mm Hg after 12 weeks. Enalapril (n = 21; titration, six patients) reduced baseline ABP from 156 +/- 12/100 +/- 9 mm Hg to 140 +/- 17/89 +/- 10 mm Hg (12 weeks). Trough-to-peak ratios in DBP were 86% for mibefradil and 75% with enalapril. Left ventricular mass (LVM) decreased from 199 +/- 65 to 193 +/- 62 g (M-mode modified American Society of Echocardiography (ASE)) and from 184 +/- 65 to 173 +/- 50 g (truncated ellipsoid method) after 12 weeks in response to mibefradil (p > 0.2), and from 212 +/- 50 to 196 +/- 57 g and from 182 +/- 39 to 170 +/- 40 g (mean +/- SD, p < 0.02) with enalapril. Mibefradil matched enalapril in 24-h ABP control. Enalapril reduced LVM significantly after 12 weeks (p < 0.02). Mibefradil did not significantly reduce LVM after 12 weeks.

CC Pharmacology - General 22002

Cytology - Human 02508

Biochemistry studies - General 10060

Pathology - Therapy 12512

**Cardiovascular system - General and methods 14501**

IT Major Concepts

**Cardiovascular Medicine (Human Medicine, Medical Sciences);**

Pharmacology

IT Diseases

**hypertension: vascular disease**

**Hypertension (MeSH)**

IT Chemicals & Biochemicals

**mibefradil: antihypertensive-drug, calcium channel blocker-drug,  
selective T-channel inhibitor**

IT Miscellaneous Descriptors

left ventricular mass; 24-hour blood pressure control

ORGN Classifier

Hominidae 86215

Super Taxa

Primates; Mammalia; Vertebrata; Chordata; Animalia

Organism Name

human: patient

Taxa Notes

Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 116644-53-2 (mibefradil)

7440-70-2 (**CALCIUM**)

75847-73-3 (**ENALAPRIL**)

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STN

ACCESSION NUMBER: 1999:216730 BIOSIS

DOCUMENT NUMBER: PREV199900216730

TITLE: Metabolic interactions between mibefradil and HMG-CoA  
reductase inhibitors: An in vitro investigation with human  
liver preparations.

AUTHOR(S): Prueksaritanont, Thomayant [Reprint author]; Ma, Bennett;  
Tang, Cuyue; Meng, Yuan; Assang, Carol; Lu, Ping; Reider,  
Paul J.; Lin, Jiunn H.; Baillie, Thomas A.

CORPORATE SOURCE: Department of Drug Metabolism, Merck Research Laboratories,  
WP 75-100, West Point, PA, 19486, USA

SOURCE: British Journal of Clinical Pharmacology, (March, 1999)  
Vol. 47, No. 3, pp. 291-298. print.

CODEN: BCPHBM. ISSN: 0306-5251.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 26 May 1999

Last Updated on STN: 26 May 1999

ED Entered STN: 26 May 1999

Last Updated on STN: 26 May 1999

- AB Aims: To determine the effects of mibefradil on the metabolism in human liver microsomal preparations of the HMG-CoA reductase inhibitors simvastatin, lovastatin, atorvastatin, cerivastatin and fluvastatin. Methods: Metabolism of the above five statins (0.5, 5 or 10  $\mu\text{M}$ ), as well as of specific CYP3A4/5 and CYP2C8/9 marker substrates, was examined in human liver microsomal preparations in the presence and absence of mibefradil (0.1-50  $\mu\text{M}$ ). Results: Mibefradil inhibited, in a concentration-dependent fashion, the metabolism of the four statins (simvastatin, lovastatin, atorvastatin and cerivastatin) known to be substrates for CYP3A. The potency of inhibition was such that the  $\text{IC}_{50}$  values ( $<1 \mu\text{M}$ ) for inhibition of all of the CYP3A substrates fell within the therapeutic plasma concentrations of mibefradil, and was comparable with that of ketoconazole. However, the inhibition by mibefradil, unlike that of ketoconazole, was at least in part mechanism-based. Based on the kinetics of its inhibition of hepatic testosterone 6 $\beta$ -hydroxylase activity, mibefradil was judged to be a powerful mechanism-based inhibitor of CYP3A4/5, with values for Kinactivation,  $K_i$  and partition ratio (moles of mibefradil metabolized per moles of enzyme inactivated) of 0.4  $\text{min}^{-1}$ , 2.3  $\mu\text{M}$  and 1.7, respectively. In contrast to the results with substrates of CYP3A, metabolism of fluvastatin, a substrate of CYP2C8/9, and the hydroxylation of tolbutamide, a functional probe for CYP2C8/9, were not inhibited by mibefradil. Conclusions: Mibefradil, at therapeutically relevant concentrations, strongly suppressed the metabolism in human liver microsomes of simvastatin, lovastatin, atorvastatin and cerivastatin through its inhibitory effects on CYP3A4/5, while the effects of mibefradil on fluvastatin, a substrate for CYP2C8/9, were minimal in this system. Since mibefradil is a potent mechanism-based inhibitor of CYP3A4/5, it is anticipated that clinically significant drug-drug interactions will likely ensue when mibefradil is coadministered with agents which are cleared primarily by CYP3A-mediated pathways.
- CC Pharmacology - General 22002  
 Biochemistry studies - General 10060  
 Enzymes - General and comparative studies: coenzymes 10802  
 Metabolism - General metabolism and metabolic pathways 13002  
 Digestive system - General and methods 14001  
**Cardiovascular system - General and methods 14501**
- IT Major Concepts  
 Metabolism; Pharmacology
- IT Parts, Structures, & Systems of Organisms  
 liver: digestive system
- IT Chemicals & Biochemicals  
 atorvastatin: HMG CoA reductase inhibitor-drug, metabolism;  
 cerivastatin: HMG CoA reductase inhibitor-drug, metabolism; cytochrome P-450 2C8/9; cytochrome P-450 3A4/5; fluvastatin: HMG CoA reductase inhibitor-drug, metabolism; lovastatin: HMG CoA reductase inhibitor-drug, metabolism; **mibefradil: antihypertensive-drug, calcium channel blocker-drug**; simvastatin: HMG CoA reductase inhibitor-drug, metabolism
- IT Miscellaneous Descriptors  
 drug-drug interactions
- ORGN Classifier  
 Hominidae 86215  
 Super Taxa  
 Primates; Mammalia; Vertebrata; Chordata; Animalia  
 Organism Name  
 human  
 Taxa Notes  
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates
- RN 134523-00-5 (atorvastatin)

145599-86-6 (cerivastatin)  
 93957-54-1 (fluvastatin)  
 75330-75-5 (lovastatin)  
 116644-53-2 (mibefradil)  
 79902-63-9 (simvastatin)  
 7440-70-2 (**CALCIUM**)  
 9028-35-7Q (HMG-COA REDUCTASE)  
 9035-51-2 (CYTOCHROME P-450)  
 37250-24-1Q (HMG-COA REDUCTASE)

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ACCESSION NUMBER: 1999:259183 BIOSIS  
 DOCUMENT NUMBER: PREV199900259183  
 TITLE: Mibefradil, a potent CYP3A inhibitor, does not alter  
 pravastatin pharmacokinetics.  
 AUTHOR(S): Becquemont, Laurent [Reprint author]; Funck-Brentano,  
 Christian; Jaillon, Patrice  
 CORPORATE SOURCE: Service de Pharmacologie, CHU Saint Antoine, Universite  
 Paris VI, 27 rue de Chaligny, 75012, Paris, France  
 SOURCE: Fundamental and Clinical Pharmacology, (1999) Vol. 13, No.  
 2, pp. 232-236. print.  
 ISSN: 0767-3981.  
 DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 2 Jul 1999  
 Last Updated on STN: 2 Jul 1999

ED Entered STN: 2 Jul 1999

Last Updated on STN: 2 Jul 1999

AB Dramatic drug-drug interactions have been observed between several HMG-CoA  
 reductase inhibitors and cytochrome P450 3A (CYP3A) inhibitors. The aim  
 of the present study was to investigate the effects of mibefradil, a  
 potent CYP3A inhibitor, on pravastatin pharmacokinetics. 12 healthy  
 volunteers were included in this open-label one-period study. Pravastatin  
 pharmacokinetics (following a single oral dose of 40 mg) was studied in  
 the absence of mibefradil (day 1) and after repeated doses (100 mg/day) of  
 mibefradil (day 8). Pravastatin pharmacokinetics after repeated doses of  
 40 mg/day was also studied in association with repeated doses (100 mg/day)  
 of mibefradil (day 16). Pravastatin area under the plasma concentration  
 vs. time curve (AUC<sub>0-infin</sub>) and C<sub>max</sub> in the absence of mibefradil on day 1  
 (170 (117 to 395) ng h/mL and 91 (72 to 200) ng/mL respectively, geometric  
 mean (95% confidence intervals)) were not significantly altered in the  
 presence of mibefradil on day 8 (224 (174 to 381) ng h/mL and 124 (72 to  
 200) ng/mL) and on day 16 (200 (137 to 555) ng h/mL and 91 (74 to 184)  
 ng/mL). T<sub>max</sub> of pravastatin in the absence of mibefradil (0.9 +/- 0.1 h,  
 arithmetic mean +/- SD) was slightly delayed in the presence of mibefradil  
 on day 8 and 16 (1.1 +/- 0.3 and 1.2 +/- 0.3 h respectively, p < 0.01 for  
 both comparisons). The results of the present study confirm the lack of  
 pharmacokinetic interactions between mibefradil and pravastatin and  
 indicate that pravastatin may be safely prescribed in the presence of  
 potent CYP3A inhibitors.

CC Pharmacology - General 22002

Biochemistry studies - General 10060

Enzymes - General and comparative studies: coenzymes 10802

Metabolism - General metabolism and metabolic pathways 13002

**Cardiovascular system - General and methods 14501**

IT Major Concepts

Pharmacology

IT Chemicals & Biochemicals

cytochrome P450 3A: inhibition; mibefradil: antihypertensive-drug,

**calcium channel blocker-drug; pravastatin: HMG CoA reductase inhibitor-drug, pharmacokinetics**

IT Miscellaneous Descriptors  
drug-drug interaction

ORGN Classifier  
Hominidae 86215  
Super Taxa  
Primates; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
human  
Taxa Notes  
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 329322-82-9 (cytochrome P450 3A)  
116644-53-2 (mibefradil)  
81093-37-0 (pravastatin)  
7440-70-2 (**CALCIUM**)  
9028-35-7Q (HMG COA REDUCTASE)  
9035-51-2 (CYTOCHROME P450)  
37250-24-1Q (HMG COA REDUCTASE)

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ACCESSION NUMBER: 1999:259181 BIOSIS  
DOCUMENT NUMBER: PREV199900259181  
TITLE: Comparative effects of mibefradil and other **calcium** antagonists on resistance arteries of different end organs.  
AUTHOR(S): van der Lee, Robin [Reprint author]; Pfaffendorf, Martin [Reprint author]; van Zwieten, Pieter A. [Reprint author]  
CORPORATE SOURCE: Department of Pharmacotherapy, Academic Medical Center, Meibergdreef 15, 1105 AZ, Amsterdam, Netherlands  
SOURCE: Fundamental and Clinical Pharmacology, (1999) Vol. 13, No. 2, pp. 198-203. print.  
ISSN: 0767-3981.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
ENTRY DATE: Entered STN: 2 Jul 1999  
Last Updated on STN: 2 Jul 1999

ED Entered STN: 2 Jul 1999  
Last Updated on STN: 2 Jul 1999

AB The biphasic contractile responses of rat isolated mesenteric, renal, coronary and basilar small arteries to potassium-induced depolarization were investigated. The tonic phase is assumed to be exclusively the result of L-type calcium channel (LCC) activation, whereas in the generation of the phasic phase T-type calcium channels (TCC) may be involved. In order to evaluate whether TCC blockade has any influence on depolarization-induced contractions the effects of the LCC antagonists nifedipine, diltiazem and verapamil were compared with those of the combined L- and TCC antagonist mibefradil. Small arteries (size 393.6 +- 4.8  $\mu$ m, n = 104) were dissected from the respective organs on male Wistar rats (300-350 g) and studied in an isometric wire myograph. The effects of increasing concentrations of the calcium antagonists on repetitive potassium-induced contractions were quantified by means of cumulative concentration-response curves. A comparison was made with mesenteric vessels of SHR and WKY for nifedipine and mibefradil. Nifedipine was the most potent compound in blocking both the phasic phase (reduction 66-77%) and the tonic phase (IC<sub>50</sub> = 1.1-5.4 nM). The effect of mibefradil on the phasic response was comparable to that of verapamil and diltiazem. With respect to the tonic response mibefradil was comparable to verapamil (IC<sub>50</sub> = 19.6-178.9 nM). These findings indicate that the TCC blockade does not contribute to the vasodilator effect of mibefradil under the conditions

investigated.

CC **Cardiovascular system - General and methods** 14501  
 Biochemistry studies - General 10060  
 Pharmacology - General 22002

IT Major Concepts  
**Cardiovascular System (Transport and Circulation);**  
 Pharmacology

IT Parts, Structures, & Systems of Organisms  
 resistance arteries: circulatory system

IT Diseases  
**hypertension: vascular disease**  
**Hypertension (MeSH)**

IT Chemicals & Biochemicals  
**diltiazem: antihypertensive-drug, calcium channel blocker-drug**  
**; mibefradil: antihypertensive-drug, calcium channel blocker-drug,**  
**vasodilator-drug; nifedipine: antihypertensive-drug, calcium**  
**channel blocker-drug; potassium; verapamil:**  
**antihypertensive-drug, calcium channel blocker-drug; L-type**  
**calcium channels; T-type calcium**  
**channels**

ORGN Classifier  
 Muridae 86375  
 Super Taxa  
 Rodentia; Mammalia; Vertebrata; Chordata; Animalia  
 Organism Name  
 SHR [spontaneously **hypertensive** rat]  
 Wistar rat  
 Taxa Notes  
 Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,  
 Rodents, Vertebrates

RN 42399-41-7 (diltiazem)  
 116644-53-2 (mibefradil)  
 21829-25-4 (nifedipine)  
 7440-09-7 (potassium)  
 52-53-9 (verapamil)  
 7440-70-2 (**CALCIUM**)

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ACCESSION NUMBER: 1999:496059 BIOSIS  
 DOCUMENT NUMBER: PREV199900496059  
 TITLE: Pharmacokinetic and pharmacodynamic aspects of concomitant  
 mibefradil-digoxin therapy at therapeutic doses.  
 AUTHOR(S): Peters, J.; Welker, H. A. [Reprint author]; Bullingham, R.  
 CORPORATE SOURCE: F. Hoffmann-La Roche, PDC5 Bldg 52/901, CH-4002, Basel,  
 Switzerland  
 SOURCE: European Journal of Drug Metabolism and Pharmacokinetics,  
 (1999) Vol. 24, No. 2, pp. 133-140. print.  
 ISSN: 0378-7966.  
 DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 23 Nov 1999  
 Last Updated on STN: 23 Nov 1999

ED Entered STN: 23 Nov 1999  
 Last Updated on STN: 23 Nov 1999

AB This study investigated the effect of mibefradil on digoxin  
 pharmacokinetics and pharmacodynamics. Following a loading dose of digoxin  
 (0.375 mg, three times, day 1), 0.375 mg was administered once daily to 40  
 healthy subjects (days 2-15). Mibefradil was administered daily at 50 mg,  
 100 mg, or 150 mg (days 9-15). With co-administration of 50 mg or 100 mg

mibefradil (the recommended doses), mean digoxin Cmax values increased 1.19- and 1.32-fold, respectively; Cmin values were 0.95- and 1.04-fold, respectively; mean AUC0-24h increased 1.05- and 1.11-fold, respectively; and the total amount of digoxin excreted in urine remained unchanged. Digoxin monotherapy produced modest but transient prolongations of PQ interval, small decreases in heart rate, and no changes in blood pressure. With the addition of **mibefradil**, no effects on trough blood pressure or **cardiac** index were observed, but there was a further increase in PQ interval and decrease in heart rate. In a previous study, mibefradil had no significant effect on trough plasma digoxin concentration in patients with congestive heart failure and ischemia. Therefore, while the vast majority of patients should not need their digoxin dosages adjusted when given mibefradil, an occasional patient may require dose reductions based on clinical response and plasma digoxin.

CC Pharmacology - General 22002  
 Biochemistry studies - General 10060  
 Biophysics - General 10502  
 Pathology - Therapy 12512  
 Metabolism - General metabolism and metabolic pathways 13002  
**Cardiovascular system - General and methods 14501**  
 Blood - General and methods 15001  
 IT Major Concepts  
   Biochemistry and Molecular Biophysics; **Cardiovascular System (Transport and Circulation)**; Pharmacology  
 IT Diseases  
   congestive **heart** failure: **heart** disease  
     **Heart** Failure, Congestive (MeSH)  
 IT Diseases  
   **ischemic heart disease: heart** disease  
     Myocardial Infarction (MeSH)  
 IT Chemicals & Biochemicals  
   digoxin: dosage, plasma, pharmacokinetics, pharmacodynamics;  
   **mibefradil: calcium channel antagonist, dosage, pharmacodynamics, plasma, pharmacokinetics**  
 IT Miscellaneous Descriptors  
   drug-drug interaction  
 ORGN Classifier  
   Hominidae 86215  
   Super Taxa  
     Primates; Mammalia; Vertebrata; Chordata; Animalia  
   Organism Name  
     human: patient  
   Taxa Notes  
     Animals, Chordates, Humans, Mammals, Primates, Vertebrates  
 RN 20830-75-5 (digoxin)  
 116644-53-2 (mibefradil)

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ACCESSION NUMBER: 1999:33514 BIOSIS

DOCUMENT NUMBER: PREV199900033514

TITLE: T-Channel-selective **calcium channel** blockade: A review of published data and therapeutic potential.

AUTHOR(S): Van Der Vring, Jan A.; Cleophas, Ton J. [Reprint author]; Van Der Wall, Ernst E.; Niemeyer, Menco G.

CORPORATE SOURCE: Merwede Hosp., P.O. Box 306, 3300 AH Dordrecht, Netherlands  
 SOURCE: Current Therapeutic Research, (Nov., 1998) Vol. 59, No. 11, pp. 754-761. print.

CODEN: CTCEA9. ISSN: 0011-393X.

DOCUMENT TYPE: Article  
 General Review; (Literature Review)

LANGUAGE: English

ENTRY DATE: Entered STN: 3 Feb 1999  
 Last Updated on STN: 3 Feb 1999

ED Entered STN: 3 Feb 1999  
 Last Updated on STN: 3 Feb 1999

AB Preclinical as well as short-term clinical trials of **mibefradil**, a **T-channel-selective calcium channel** blocker, are reviewed. **Mibefradil** reduced afterload and was effective in reducing **hypertension** and stable **angina pectoris**. It did not display any relevant negative inotropic or positive chronotropic effect. Because **mibefradil** has been withdrawn from the market by the manufacturer as a result of a drug interaction involving the cytochrome P-450 3A4 enzyme, it is hoped that new T-channel-selective calcium channel blockers will be developed to further explore this promising, but thus far preliminarily tested therapeutic option.

CC Pharmacology - General 22002  
 Biochemistry studies - General 10060  
 Enzymes - General and comparative studies: coenzymes 10802  
 Pathology - Therapy 12512  
**Cardiovascular system - General and methods 14501**  
 Toxicology - General and methods 22501

IT Major Concepts  
**Cardiovascular System (Transport and Circulation);**  
 Pharmacology

IT Diseases  
**hypertension: vascular disease**  
**Hypertension (MeSH)**

IT Diseases  
 stable **angina pectoris: heart disease, vascular disease**  
**Angina Pectoris (MeSH)**

IT Chemicals & Biochemicals  
**calcium channel: T-channel-selective blockade; cytochrome P-450 3A4; mibefradil: antihypertensive-drug, cardiovascular-drug, calcium channel blocker-drug, T-channel-selective**

IT Miscellaneous Descriptors  
 drug-drug interaction

ORGN Classifier  
 Animalia 33000  
 Super Taxa  
 Animalia  
 Organism Name  
 animal: animal model  
 Taxa Notes  
 Animals

ORGN Classifier  
 Hominidae 86215  
 Super Taxa  
 Primates; Mammalia; Vertebrata; Chordata; Animalia  
 Organism Name  
 human: patient  
 Taxa Notes  
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 329736-03-0 (cytochrome P-450 3A4)  
 116644-53-2 (mibefradil)  
 7440-70-2 (**CALCIUM**)  
 9035-51-2 (CYTOCHROME P-450)



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ACCESSION NUMBER: 1998:484837 BIOSIS  
DOCUMENT NUMBER: PREV199800484837  
TITLE: The relevance of T-type calcium antagonists: A  
profile of mibefradil.  
AUTHOR(S): Glasser, Stephen P. [Reprint author]  
CORPORATE SOURCE: Div. Clinical Pharmacology, Univ. South Fla., 3500 E.  
Fletcher Avenue, Suite 218, Tampa, FL 33613, USA  
SOURCE: Journal of Clinical Pharmacology, (Aug., 1998) Vol. 38, No.  
8, pp. 659-669. print.  
CODEN: JPCPBR. ISSN: 0091-2700.  
DOCUMENT TYPE: Article  
General Review; (Literature Review)  
LANGUAGE: English  
ENTRY DATE: Entered STN: 5 Nov 1998  
Last Updated on STN: 5 Nov 1998

ED Entered STN: 5 Nov 1998

Last Updated on STN: 5 Nov 1998

AB L- and T-type voltage-dependent transmembrane calcium channels are important for normal functioning of the cardiovascular system. T-type channels are heterogeneous group, and have physiologic and pathophysiologic relevance in a number of organ systems, including the heart and central nervous system. They appear to be involved in the control of blood pressure in patients with essential hypertension and in protection from ischemic damage. Alterations of both L- and T-type calcium channels are involved in the development of hypertension. Pharmacologic modulation of T-type calcium channels appears to reduce membrane calcium flux and ameliorate hypertension. During early ischemic damage, T-type calcium channels appear to remain functional whereas L-type channels are already inactivated. T-type calcium channels also appear to be involved in the development of supraventricular arrhythmias, some forms of arrhythmias in cardiomyopathy, and cardiac hypertrophy. The heterogeneity of T-type calcium channels should make it possible to target drugs to specific subgroups of T-type calcium channels. A new class of calcium antagonist, the benzimidazolyl-substituted tetraline derivatives, has been shown to block both L- and T-type calcium channels. The first member of this class approved for clinical use is mibefradil. Clinical studies have demonstrated the efficacy of mibefradil in lowering blood pressure and as an antianginal and anti-ischemic agent. At clinically recommended doses, mibefradil has a heart rate lowering effect without a negative inotropic effect, and a favorable side effect profile. Because it is metabolized by the cytochrome P450 pathway, it should be used cautiously with other agents similarly metabolized.

CC Pharmacology - Cardiovascular system 22010  
Biophysics - Membrane phenomena 10508  
Cardiovascular system - Heart pathology 14506  
Cardiovascular system - Blood vessel pathology 14508  
Biochemistry studies - General 10060  
Biochemistry studies - Minerals 10069

IT Major Concepts  
Cardiovascular System (Transport and Circulation);  
Pharmacology

IT Diseases  
arrhythmia: heart disease  
Arrhythmia (MeSH)

IT Diseases  
hypertension: vascular disease  
Hypertension (MeSH)

IT Chemicals & Biochemicals  
     **calcium channel; mibefradil: antiarrhythmic-drug, antihypertensive-drug, calcium channel blocker-drug**

ORGN Classifier  
     Muridae 86375  
     Super Taxa  
         Rodentia; Mammalia; Vertebrata; Chordata; Animalia  
     Organism Name  
         mouse  
     Taxa Notes  
         Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 116644-53-2 (mibefradil)  
     7440-70-2 (**CALCIUM**)

L103 ANSWER 156 OF 198 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1999:9651 BIOSIS  
 DOCUMENT NUMBER: PREV199900009651  
 TITLE: **Mibefradil prevents L-name-exacerbated nephrosclerosis in spontaneously hypertensive rats (SHR).**

AUTHOR(S): Qiu, C. [Reprint author]; Roeckel, A. [Reprint author]; Bruneval, P.; Heudes, D. [Reprint author]; Roux, S. [Reprint author]

CORPORATE SOURCE: F. Hoffmann-La Roche Ltd., Basel, Switzerland  
 SOURCE: Journal of the American Society of Nephrology, (Sept., 1998) Vol. 9, No. PROGRAM AND ABSTR. ISSUE, pp. 619A. print.  
 Meeting Info.: 31st Annual Meeting of the American Society of Nephrology. Philadelphia, Pennsylvania, USA. October 25-28, 1998. American Society of Nephrology.  
 CODEN: JASNEU. ISSN: 1046-6673.

DOCUMENT TYPE: Conference; (Meeting)  
 Conference; Abstract; (Meeting Abstract)  
 Conference; (Meeting Poster)

LANGUAGE: English  
 ENTRY DATE: Entered STN: 11 Jan 1999  
 Last Updated on STN: 11 Jan 1999

ED Entered STN: 11 Jan 1999  
 Last Updated on STN: 11 Jan 1999

CC Pharmacology - General 22002  
     **Cardiovascular system - General and methods 14501**  
     Urinary system - General and methods 15501  
     General biology - Symposia, transactions and proceedings 00520  
     Biochemistry studies - General 10060

IT Major Concepts  
     Pharmacology; Urinary System (Chemical Coordination and Homeostasis)

IT Diseases  
     chronic renal failure: urologic disease  
     Kidney Failure, Chronic (MeSH)

IT Diseases  
     **hypertension: vascular disease**  
     **Hypertension (MeSH)**

IT Diseases  
     nephrosclerosis: urologic disease, vascular disease, L-name-exacerbated  
     Nephrosclerosis (MeSH)

IT Chemicals & Biochemicals  
     cilazapril: angiotensin-converting enzyme inhibitor-drug;  
     **mibefradil: renal-acting-drug, calcium channel blocker, renal**

**protective effects**

IT Miscellaneous Descriptors  
Meeting Abstract; Meeting Poster

ORGN Classifier  
Muridae 86375  
Super Taxa  
Rodentia; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
rat: animal model, spontaneously **hypertensive**  
Taxa Notes  
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,  
Rodents, Vertebrates

RN 88768-40-5 (cilazapril)  
116644-53-2 (mibefradil)  
7440-70-2 (**CALCIUM**)  
9015-82-1 (ANGIOTENSIN-CONVERTING ENZYME)

L103 ANSWER 157 OF 198 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on  
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ACCESSION NUMBER: 1999:9624 BIOSIS  
DOCUMENT NUMBER: PREV199900009624  
TITLE: Comparative effects of 'T' and 'L' type **calcium**  
**channel** blockade in the remnant kidney (RK) model.

AUTHOR(S): Griffin, K. A. [Reprint author]; Picken, M.; Bakris, G. L.;  
Bidani, A. K.

CORPORATE SOURCE: Loyola Univ. and Hines VA, Maywood, IL, USA  
SOURCE: Journal of the American Society of Nephrology, (Sept.,  
1998) Vol. 9, No. PROGRAM AND ABSTR. ISSUE, pp. 610A.  
print.  
Meeting Info.: 31st Annual Meeting of the American Society  
of Nephrology. Philadelphia, Pennsylvania, USA. October  
25-28, 1998. American Society of Nephrology.  
CODEN: JASNEU. ISSN: 1046-6673.

DOCUMENT TYPE: Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 11 Jan 1999  
Last Updated on STN: 11 Jan 1999

ED Entered STN: 11 Jan 1999  
Last Updated on STN: 11 Jan 1999

CC Urinary system - General and methods 15501  
Pathology - Therapy 12512  
**Cardiovascular system - General and methods 14501**  
Pharmacology - General 22002  
General biology - Symposia, transactions and proceedings 00520

IT Major Concepts  
**Cardiovascular System (Transport and Circulation);**  
Pharmacology; Urinary System (Chemical Coordination and Homeostasis)

IT Diseases  
chronic renal failure: urologic disease  
Kidney Failure, Chronic (MeSH)

IT Diseases  
glomerulosclerosis: urologic disease  
Glomerulosclerosis, Focal (MeSH)

IT Chemicals & Biochemicals  
**mibefradil: antihypertensive-drug, calcium channel blocker-drug**  
**; L-type calcium channel; T-type calcium**  
**channel**

IT Miscellaneous Descriptors  
blood pressure; renal autoregulation; Meeting Abstract

ORGN Classifier  
Muridae 86375  
Super Taxa  
Rodentia; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
rat: remnant kidney model  
Taxa Notes  
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,  
Rodents, Vertebrates  
RN 116644-53-2 (mibefradil)  
7440-70-2 (**CALCIUM**)

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ACCESSION NUMBER: 1999:67205 BIOSIS

DOCUMENT NUMBER: PREV199900067205

TITLE: Antioxidative action of the novel **calcium**  
**channel** antagonist **mibefradil** on  
low-density lipoproteins.

AUTHOR(S): Leonhardt, W. [Reprint author]; Lange, M.

CORPORATE SOURCE: Inst. Policlin. Clin. Metabolic Res., Technical Univ.  
Dresden, Fetscherstrasse 74, D-01307 Dresden, Germany

SOURCE: European Journal of Clinical Pharmacology, (Oct., 1998)  
Vol. 54, No. 8, pp. 603-607. print.  
CODEN: EJCPAS. ISSN: 0031-6970.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 16 Feb 1999

Last Updated on STN: 16 Feb 1999

ED Entered STN: 16 Feb 1999

Last Updated on STN: 16 Feb 1999

AB Objective: **Mibefradil** is a novel **calcium**

**channel** antagonist that selectively blocks T-channels. It acts to  
reduce hypertension, is cardioprotective and reduces ischemic episodes.  
Oxidative modification of low-density lipoproteins (LDL) is well known to  
contribute to coronary atherosclerosis and we therefore investigated to  
see whether mibefradil had antioxidative action on LDL. Methods: Human  
LDL were isolated by ultracentrifugation. In vitro oxidation of LDL (0.1  
mumol cntdot 1-1 protein) in the presence of various concentrations of  
mibefradil was initiated by 3.2 mumol cntdot 1-1 copper ions. The  
kinetics of formation of conjugated dienes was followed photometrically.  
Malondialdehyde and lipoperoxides were determined at maximum oxidation.  
LDL (0.3 mumol cntdot 1-1) were also pre-incubated with mibefradil (120  
mumol cntdot 1-1). Excessive mibefradil was separated by column  
technique. The resultant LDL were oxidized using copper ions or (AAPH)  
2,2'-azobis(2-amidinopropane) hydrochloride. Results: The presence of  
mibefradil in the concentration range from 10 to 200 mumol cntdot 1-1 had  
dose-dependent effects. These were protection of LDL against oxidation  
measured as prolongation of the lagtime up to 250%, and reduction in the  
formation of malondialdehyde down to 65% and of lipoperoxides to 20%.  
Pre-incubation of LDL with mibefradil prolonged the lagtime of Cu-mediated  
oxidation up to 132% and of AAPH-mediated oxidation up to 138%.

Conclusion: In addition to the T-channel blocking and antiproliferative  
effects, our results provide arguments for a protective role of mibefradil  
(10-200 mumol cntdot 1-1) on LDL against in vitro oxidation. This was  
shown with three independent parameters (lagtime, malondialdehyde and  
lipoperoxides) and in different oxidation models.

CC Pharmacology - Cardiovascular system 22010

Biophysics - Membrane phenomena 10508

**Cardiovascular system - Heart pathology 14506**

**Cardiovascular system - Blood vessel pathology 14508**  
 Pharmacology - Clinical pharmacology 22005  
 Biochemistry studies - General 10060  
 Biochemistry studies - Proteins, peptides and amino acids 10064  
 Biochemistry studies - Minerals 10069  
 IT Major Concepts  
     **Cardiovascular Medicine (Human Medicine, Medical Sciences);**  
     Pharmacology  
 IT Diseases  
     atherosclerosis: vascular disease  
     Arteriosclerosis (MeSH)  
 IT Chemicals & Biochemicals  
     low-density lipoprotein; **mibefradil: antihypertensive-drug,**  
     **calcium channel blocker-drug, antioxidant, cardioprotectant**  
 ORGN Classifier  
     Hominidae 86215  
     Super Taxa  
         Primates; Mammalia; Vertebrata; Chordata; Animalia  
     Organism Name  
         human  
     Taxa Notes  
         Animals, Chordates, Humans, Mammals, Primates, Vertebrates  
 RN 116644-53-2 (mibefradil)  
     7440-70-2 (**CALCIUM**)

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ACCESSION NUMBER: 1998:524258 BIOSIS  
 DOCUMENT NUMBER: PREV199800524258  
 TITLE: Effect of **mibefradil** on daily ischaemic episodes  
     with and without increase in **heart** rate.  
 AUTHOR(S): Tzivoni, Dan; Gilula, Zvi; Klutstein, Marc; Reisin,  
     Leonardo; Botvin, Shulamit; Kobrin, Isaac  
 CORPORATE SOURCE: Shaare Zedek Med. Cent., Jerusalem, Israel  
 SOURCE: European Heart Journal, (Aug., 1998) Vol. 19, No. ABST.  
     SUPPL., pp. 511. print.  
     Meeting Info.: XXth Congress of the European Society of  
     Cardiology. Vienna, Austria. August 22-26, 1998. European  
     Society of Cardiology.  
     CODEN: EHJODF. ISSN: 0195-668X.  
 DOCUMENT TYPE: Conference; (Meeting)  
     Conference; Abstract; (Meeting Abstract)  
     Conference; (Meeting Poster)  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 22 Dec 1998  
     Last Updated on STN: 22 Dec 1998  
 ED Entered STN: 22 Dec 1998  
     Last Updated on STN: 22 Dec 1998  
 CC **Cardiovascular system - Heart pathology 14506**  
     **Cardiovascular system - Blood vessel pathology 14508**  
     Pharmacology - Clinical pharmacology 22005  
     Pharmacology - Cardiovascular system 22010  
     General biology - Symposia, transactions and proceedings 00520  
     Biochemistry studies - General 10060  
 IT Major Concepts  
     **Cardiovascular Medicine (Human Medicine, Medical Sciences);**  
     Pharmacology  
 IT Diseases  
     **ischemia: vascular disease**  
     **Ischemia (MeSH)**

IT Chemicals & Biochemicals  
**mibefradil: antianginal-drug, calcium channel blocker-drug**

IT Miscellaneous Descriptors  
**heart** rate; Meeting Abstract; Meeting Poster

ORGN Classifier  
Hominidae 86215  
Super Taxa  
Primates; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
human  
Taxa Notes  
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 116644-53-2 (mibefradil)  
7440-70-2 (**CALCIUM**)

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ACCESSION NUMBER: 1998:524254 BIOSIS  
DOCUMENT NUMBER: PREV199800524254  
TITLE: The effects of **mibefradil** on left ventricular  
perfusion in patients with chronic stable **angina**  
pectoris.

AUTHOR(S): Tartagni, F. [Reprint author]; Fallani, F. [Reprint  
author]; Farneti, L. [Reprint author]; Monetti, N.; Fanti,  
S.; Guidalotti, P. L.; Ghezzi, C.; Magnani, B. [Reprint  
author]

CORPORATE SOURCE: Ist. Malattie Apparato Cardiovasc., Univ. Studi, Bologna,  
Italy

SOURCE: European Heart Journal, (Aug., 1998) Vol. 19, No. ABST.  
SUPPL., pp. 510. print.  
Meeting Info.: XXth Congress of the European Society of  
Cardiology. Vienna, Austria. August 22-26, 1998. European  
Society of Cardiology.  
CODEN: EHJODF. ISSN: 0195-668X.

DOCUMENT TYPE: Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
Conference; (Meeting Poster)

LANGUAGE: English

ENTRY DATE: Entered STN: 22 Dec 1998  
Last Updated on STN: 22 Dec 1998

ED Entered STN: 22 Dec 1998  
Last Updated on STN: 22 Dec 1998

CC **Cardiovascular system - Heart pathology 14506**  
Biophysics - Membrane phenomena 10508  
**Cardiovascular system - Physiology and biochemistry 14504**  
**Cardiovascular system - Blood vessel pathology 14508**  
Pharmacology - Clinical pharmacology 22005  
Pharmacology - Cardiovascular system 22010  
General biology - Symposia, transactions and proceedings 00520  
Biochemistry studies - General 10060  
Biochemistry studies - Minerals 10069

IT Major Concepts  
**Cardiovascular Medicine (Human Medicine, Medical Sciences);**  
Pharmacology

IT Diseases  
**angina pectoris: heart disease, vascular disease**  
**Angina Pectoris (MeSH)**

IT Chemicals & Biochemicals  
**mibefradil: calcium channel blocker-drug, vasodilator-drug**

IT Miscellaneous Descriptors

myocardial perfusion; Meeting Abstract; Meeting Poster  
 ORGN Classifier  
   Hominidae 86215  
   Super Taxa  
     Primates; Mammalia; Vertebrata; Chordata; Animalia  
   Organism Name  
     human: patient  
   Taxa Notes  
     Animals, Chordates, Humans, Mammals, Primates, Vertebrates  
 RN 116644-53-2 (mibefradil)  
   7440-70-2 (CALCIUM)

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ACCESSION NUMBER: 1999:34139 BIOSIS  
 DOCUMENT NUMBER: PREV199900034139  
 TITLE: Profound symptomatic bradycardia associated with combined  
   mibefradil and beta-blocker therapy.  
 AUTHOR(S): Rogers, Ian R. [Reprint author]; Prpic, Ross  
 CORPORATE SOURCE: Sir Charles Gairdner Hosp., Verdun St., Nedlands, WA 6009,  
   Australia  
 SOURCE: Medical Journal of Australia, (Oct. 19, 1998) Vol. 169, No.  
   8, pp. 425-427. print.  
   CODEN: MJAUAJ. ISSN: 0025-729X.  
 DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 3 Feb 1999  
   Last Updated on STN: 3 Feb 1999

ED Entered STN: 3 Feb 1999

Last Updated on STN: 3 Feb 1999

AB We report two cases where the addition of **mibefradil** to long  
 term beta-blocker therapy in managing **hypertension** produced  
 profound symptomatic bradycardia requiring cardiac pacing. Reports of a  
 number of interactions between **mibefradil** and other  
**cardioactive** drugs have now led to its withdrawal from the market  
 worldwide.

CC Toxicology - General and methods 22501  
   **Cardiovascular system - General and methods 14501**  
   Pharmacology - General 22002

IT Major Concepts  
   **Cardiovascular Medicine (Human Medicine, Medical Sciences);**  
   Toxicology

IT Diseases  
   profound symptomatic bradycardia: **heart disease, toxicity**

IT Chemicals & Biochemicals  
   **metoprolol: antihypertensive-drug, beta-adrenergic**  
   **antagonist-drug; mibefradil: antihypertensive-drug, calcium**  
   **channel blocker-drug**

IT Methods & Equipment  
   **cardiac pacing: therapeutic method; combined**  
   **mibefradil-beta-blocker therapy: therapeutic method, toxicity**

IT Miscellaneous Descriptors  
   blood pressure; Case Study

ORGN Classifier  
   Hominidae 86215  
   Super Taxa  
     Primates; Mammalia; Vertebrata; Chordata; Animalia  
   Organism Name  
     human: elderly, middle age, patient, female  
   Taxa Notes

Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 51384-51-1 (metoprolol)  
116644-53-2 (mibefradil)  
7440-70-2 (**CALCIUM**)

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ACCESSION NUMBER: 1998:323922 BIOSIS

DOCUMENT NUMBER: PREV199800323922

TITLE: Pharmacokinetics and pharmacodynamics of **mibefradil**  
in **hypertensive** patients with varying degrees of  
renal insufficiency.

AUTHOR(S): Welker, Horst A. [Reprint author]; Weidekamm, Erhard;  
Houwing, Nathalie; De Chatel, Rudolf

CORPORATE SOURCE: F. Hoffmann-La Roche, PDC5, 52/901, CH-4002 Basel,  
Switzerland

SOURCE: Pharmacology (Basel), (June, 1998) Vol. 56, No. 6, pp.  
297-307. print.

CODEN: PHMGBN. ISSN: 0031-7012.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 22 Jul 1998

Last Updated on STN: 22 Jul 1998

ED Entered STN: 22 Jul 1998

Last Updated on STN: 22 Jul 1998

AB Mibefradil, the first member of the tetralol derivatives, a new class of  
calcium antagonists, is used for the treatment of hypertension and angina  
pectoris. This study was designed to investigate the effect of varying  
degrees of chronic renal impairment on mibefradil pharmacokinetics and  
pharmacodynamics. Neither pharmacokinetic nor pharmacodynamic parameters  
varied as a function of renal status. Additionally, hemodialysis removed  
only a relatively small fraction of drug from the body. It was concluded  
that the majority of renal-failure patients will not require a change in  
mibefradil dosage relative to patients with normal renal function.  
Following hemodialysis, supplemental mibefradil treatment should not be  
necessary.

CC Pharmacology - General 22002

Biochemistry studies - General 10060

Pathology - Therapy 12512

Metabolism - General metabolism and metabolic pathways 13002

**Cardiovascular system - General and methods 14501**

Urinary system - General and methods 15501

IT Major Concepts

**Cardiovascular Medicine (Human Medicine, Medical Sciences);**

Nephrology (Human Medicine, Medical Sciences); Pharmacology

IT Diseases

**hypertension: vascular disease**

**Hypertension (MeSH)**

IT Diseases

renal failure: urologic disease

Kidney Failure (MeSH)

IT Diseases

renal insufficiency: urologic disease

Kidney Failure (MeSH)

IT Chemicals & Biochemicals

**mibefradil: calcium channel blocker-drug, cardiovascular-drug,**

**pharmacokinetics, pharmacodynamics, dosage**

IT Methods & Equipment

hemodialysis: therapeutic method

ORGN Classifier



Hominidae 86215

Super Taxa

Primates; Mammalia; Vertebrata; Chordata; Animalia

Organism Name

human: patient

Taxa Notes

Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 116644-53-2 (mibefradil)

7440-70-2 (CALCIUM)

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ACCESSION NUMBER: 1998:515672 BIOSIS

DOCUMENT NUMBER: PREV199800515672

TITLE: Mibefradil pharmacokinetic and pharmacodynamic population analysis.

AUTHOR(S): Welker, H. A. [Reprint author]; Banken, L.

CORPORATE SOURCE: F. Hoffmann-La Roche, PDC5, 52/1208, CH-4070 Basel, Switzerland

SOURCE: International Journal of Clinical Pharmacology Research, (1998) Vol. 18, No. 2, pp. 63-71. print.  
CODEN: CPHRDE. ISSN: 0251-1649.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 18 Dec 1998

Last Updated on STN: 18 Dec 1998

ED Entered STN: 18 Dec 1998

Last Updated on STN: 18 Dec 1998

AB **Mibefradil** is a new T-channel selective

**calcium** antagonist effective in the treatment of hypertension and chronic stable angina pectoris. In this study steady-state plasma mibefradil concentrations and pharmacodynamic measurements were obtained from American and European clinical studies and analyzed using NONMEM. Doses ranged from 12.5-200 mg orally once-daily. A linear one-compartment pharmacokinetic model with first-order absorption was employed. Best parameter estimates were as follows: absorption rate-constant = 2.7 hours<sup>-1</sup>, clearance = 5.7 L/hour, volume of distribution = 179 L. The bioavailability of the 25 mg oral dose relative to higher doses was 0.83. Conclusions based on the Emax model equations were that at average plasma concentrations achieved clinically (apprx300 ng/ml and apprx600 ng/ml for 50 and 100 mg/day, respectively) the effect on heart rate is near maximum, the effect on blood pressure is about 50% of maximum, and the effect on PQ interval is small. The model also predicts that diastolic blood pressure and heart rate reductions will tend to be greater in patients with higher baseline values and with increasing mibefradil plasma concentrations. The increase in PQ interval is strongly related to plasma mibefradil concentration. The population analysis shows that mibefradil pharmacokinetics and pharmacodynamics were not affected in a clinically relevant manner by demographic characteristics.

CC Pharmacology - General 22002

Biochemistry studies - General 10060

Pathology - Therapy 12512

Metabolism - General metabolism and metabolic pathways 13002

**Cardiovascular system - General and methods 14501**

IT Major Concepts

**Cardiovascular Medicine (Human Medicine, Medical Sciences);**

Pharmacology

IT Diseases

**angina pectoris: heart disease, vascular disease****Angina Pectoris (MeSH)**

IT Diseases  
     **hypertension: vascular disease**  
     **Hypertension (MeSH)**  
 IT Chemicals & Biochemicals  
     **mibefradil: antianginal-drug, antihypertensive-drug, T-channel**  
     **selective calcium antagonist, oral administration, pharmacodynamics,**  
     **plasma, pharmacokinetics, dosage**  
 IT Miscellaneous Descriptors  
     blood pressure; **heart rate**  
 ORGN Classifier  
     Hominidae 86215  
     Super Taxa  
     Primates; Mammalia; Vertebrata; Chordata; Animalia  
     Organism Name  
     human: patient  
     Taxa Notes  
     Animals, Chordates, Humans, Mammals, Primates, Vertebrates  
 RN 116644-53-2 (mibefradil)  
     7440-70-2 (**CALCIUM**)

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ACCESSION NUMBER: 1998:329115 BIOSIS  
 DOCUMENT NUMBER: PREV199800329115  
 TITLE: Acute renal hemodynamics and **cardiovascular**  
     effects of **mibefradil**, a novel **calcium**  
     **channel** blocker, selective for T-type-Ca<sup>2+</sup>-  
     **channels**, in conscious spontaneously  
     **hypertensive** rats.  
 AUTHOR(S): Chung, O. [Reprint author]; Kuehl, H. [Reprint author];  
     Ritz, E.; Unger, T. [Reprint author]  
 CORPORATE SOURCE: Inst. Pharmacol., Univ. Kiel, Kiel, Germany  
 SOURCE: Nephrology Dialysis Transplantation, (June, 1998) Vol. 13,  
     No. 6, pp. A62. print.  
     Meeting Info.: Annual Congress of the European Renal  
     Association, European Dialysis and Transplant Association.  
     Rimini, Italy. June 6-9, 1998. European Dialysis and  
     Transplant Association; European Renal Association.  
     ISSN: 0931-0509.  
 DOCUMENT TYPE: Conference; (Meeting)  
     Conference; Abstract; (Meeting Abstract)  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 12 Aug 1998  
     Last Updated on STN: 12 Aug 1998

ED Entered STN: 12 Aug 1998  
     Last Updated on STN: 12 Aug 1998  
 CC Pharmacology - General 22002  
     **Cardiovascular system - General and methods 14501**  
     Urinary system - General and methods 15501  
     General biology - Symposia, transactions and proceedings 00520

IT Major Concepts  
     **Cardiovascular System (Transport and Circulation);**  
     Pharmacology  
 IT Chemicals & Biochemicals  
     **amlodipine: antihypertensive-drug; mibefradil: calcium**  
     **channel blocker-drug; nifedipine: antihypertensive-drug;**  
     **verapamil: antihypertensive-drug; T-type-calcium**  
     **channels**  
 IT Miscellaneous Descriptors  
     acute renal hemodynamics; **cardiovascular effects**; Meeting

## Abstract

ORGN Classifier

Muridae 86375

Super Taxa

Rodentia; Mammalia; Vertebrata; Chordata; Animalia

Organism Name

spontaneously **hypertensive** rat: conscious

Taxa Notes

Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,  
Rodents, Vertebrates

RN 88150-42-9 (amlodipine)

116644-53-2 (mibefradil)

21829-25-4 (nifedipine)

52-53-9 (verapamil)

7440-70-2 (**CALCIUM**)L103 ANSWER 165 OF 198 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on  
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ACCESSION NUMBER: 1998:207220 BIOSIS

DOCUMENT NUMBER: PREV199800207220

TITLE: Role of T **channels** in **cardiovascular**  
function.

AUTHOR(S): Hermsmeyer, Kent [Reprint author]

CORPORATE SOURCE: Oregon Reg. Primate Res. Cent., 505 NW 185th Ave.,  
Beaverton, OR 97006, USASOURCE: Cardiology, (Feb., 1998) Vol. 89, No. SUPPL. 1, pp. 2-9.  
print.

CODEN: CAGYAO. ISSN: 0008-6312.

DOCUMENT TYPE: Article

General Review; (Literature Review)

LANGUAGE: English

ENTRY DATE: Entered STN: 11 May 1998

Last Updated on STN: 11 May 1998

ED Entered STN: 11 May 1998

Last Updated on STN: 11 May 1998

AB Although two types of Ca<sup>2+</sup> channels are found to occur in the cardiovascular system, very little is known about one of them, primarily because a pharmacological blocking agent has been lacking. The enigmatic transient (T)-type Ca<sup>2+</sup> channel has finally been recognized by a selective Ca<sup>2+</sup> antagonist. The novel tetralol Ca<sup>2+</sup> antagonist, mibefradil, is a selective T-type Ca<sup>2+</sup> channel blocker that produces effective vasodilatation with additional inhibitory actions on blood vessel wall and left ventricular thickening. The availability of a blocking agent has begun to reveal the significance of T-type Ca<sup>2+</sup> channel signals. Selective T-type Ca<sup>2+</sup> channel blockade characteristics include vascular selectivity, freedom from negative cardiac inotropism, consistent and predictable reduction in heart rate, reduction in subendothelial proliferation, and increased survival of severely hypertensive and heart failure animal models. Mibefradil increases coronary blood flow without increasing myocardial oxygen consumption, and by decreasing heart rate and thus time spent in diastole, improves subendocardial perfusion. Improved perfusion of the myocardial wall and lowered heart rate appear to normalize the underlying pathophysiological factors, improve heart failure, and provide long-term protection. Thus, T-type Ca<sup>2+</sup> channel blockade offers significant new cardiovascular protective benefits, even in the presence of critical pathophysiological elements (i.e. increased heart rate and neurohumors in the presence of decreased ejection fraction and contractility) found in heart failure.

CC **Cardiovascular system - General and methods** 14501

Biochemistry studies - General 10060

Blood - General and methods 15001

IT Major Concepts  
Biochemistry and Molecular Biophysics; **Cardiovascular System**  
**(Transport and Circulation)**

IT Parts, Structures, & Systems of Organisms  
blood vessel wall: circulatory system, vasodilation; left ventricle:  
circulatory system, thickening; myocardial wall: circulatory system,  
perfusion

IT Diseases  
heart failure: heart disease  
Heart Failure, Congestive (MeSH)

IT Diseases  
hypertension: vascular disease  
Hypertension (MeSH)

IT Chemicals & Biochemicals  
calcium ion channel: T-type, cardiovascular activity, inhibition,  
transient-type; mibefradil: T-type calcium ion channel  
blocker, cardiovascular activity, vasodilator

IT Miscellaneous Descriptors  
coronary blood flow; heart rate; subendocardial perfusion

ORGN Classifier  
Animalia 33000  
Super Taxa  
Animalia  
Organism Name  
animal: animal model  
Taxa Notes  
Animals

RN 116644-53-2 (mibefradil)  
14127-61-8 (**CALCIUM** ION)

L103 ANSWER 166 OF 198 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on  
STN

ACCESSION NUMBER: 1998:9753 BIOSIS  
DOCUMENT NUMBER: PREV199800009753  
TITLE: Comparative **antihypertensive** effectiveness of  
once-daily **mibefradil** and diltiazem CD.  
AUTHOR(S): Bittar, Neville [Reprint author]  
CORPORATE SOURCE: Univ. Wisconsin, H6/354 Clin. Sci. Cent., 600 Highland  
Ave., Madison, WI 53792, USA  
SOURCE: Clinical Therapeutics, (Sept.-Oct., 1997) Vol. 19, No. 5,  
pp. 954-962. print.  
CODEN: CLTHDG. ISSN: 0149-2918.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
ENTRY DATE: Entered STN: 23 Dec 1997  
Last Updated on STN: 24 Feb 1998

ED Entered STN: 23 Dec 1997  
Last Updated on STN: 24 Feb 1998

AB This multicenter, double-masked, randomized, forced-titration,  
parallel-group trial was designed to determine whether we could confirm  
the results of a previous trial that demonstrated a significantly greater  
**antihypertensive** effect for **mibefradil** compared with  
diltiazem CD. Two hundred thirty-nine patients with uncomplicated  
mild-to-moderate essential hypertension and a baseline sitting diastolic  
blood pressure (SDBP) between 95 and 114 mm Hg were randomized to receive  
once-daily treatment with mibefradil 50 mg (n=119) or diltiazem CD 180 mg  
(n = 120). After 4 weeks of treatment, all patients underwent forced  
titration to mibefradil 100 mg or diltiazem CD 360 mg for an additional 8  
weeks. After 12 weeks of active treatment, the mean reduction from

baseline in trough SDBP was significantly greater with mibefradil than with diltiazem CD (-14.3 +/- 6.6 mm Hg vs -11.7 +/- 7.4 mm Hg, respectively). In addition, significantly more patients receiving mibefradil had a decrease in SDBP >10 mm Hg or a decrease to <90 mm Hg by week 12 than did patients receiving diltiazem CD (82% vs 72%, respectively). The tolerability of mibefradil and diltiazem CD were comparable, with similar percentages of patients in both groups reporting at least one adverse event (21% vs 22%, respectively) that was considered to be at least remotely related to the study drug. The results of this study confirm those of the previous trial. Once daily treatment with mibefradil 100 mg is significantly more effective than diltiazem CD 360 mg in lowering both diastolic and systolic blood pressure. Both drugs are well tolerated.

CC Pharmacology - Cardiovascular system 22010  
 Biochemistry studies - General 10060  
 Pathology - Therapy 12512  
**Cardiovascular system - Blood vessel pathology 14508**  
 Pharmacology - Drug metabolism and metabolic stimulators 22003  
 Pharmacology - Clinical pharmacology 22005  
 IT Major Concepts  
**Cardiovascular Medicine (Human Medicine, Medical Sciences);**  
 Pharmacology  
 IT Chemicals & Biochemicals  
**diltiazem CD: antihypertensive-drug, calcium channel blocker, once daily, effectiveness; mibefradil: antihypertensive-drug, calcium channel blocker, once daily, effectiveness**  
 ORGN Classifier  
 Hominidae 86215  
 Super Taxa  
 Primates; Mammalia; Vertebrata; Chordata; Animalia  
 Organism Name  
 human: patient  
 Taxa Notes  
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates  
 RN 116644-53-2 (mibefradil)  
 7440-70-2 (**CALCIUM**)

L103 ANSWER 167 OF 198 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1998:37469 BIOSIS  
 DOCUMENT NUMBER: PREV199800037469  
 TITLE: **Mibefradil: A new T-channel selective calcium antagonist.**  
 AUTHOR(S): Kobrin, Isaac; Charlon, Vincent; Lindberg, Elisabet; Neumann, Norbert; Pordy, Robert  
 CORPORATE SOURCE: Hoffmann-La Roche, 340 Kingsland Street, Nutley, NJ 07110, USA  
 SOURCE: Drugs of Today, (Oct., 1997) Vol. 33, No. 8, pp. 523-542. print.  
 CODEN: MDACAP. ISSN: 0025-7656.  
 DOCUMENT TYPE: Article  
 General Review; (Literature Review)  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 14 Jan 1998  
 Last Updated on STN: 14 Jan 1998  
 ED Entered STN: 14 Jan 1998  
 Last Updated on STN: 14 Jan 1998  
 CC Pharmacology - Cardiovascular system 22010  
 Biochemistry studies - Minerals 10069  
**Cardiovascular system - Heart pathology 14506**

**Cardiovascular system - Blood vessel pathology 14508**  
 Pharmacology - Clinical pharmacology 22005  
 IT Major Concepts  
     **Cardiovascular Medicine (Human Medicine, Medical Sciences);**  
     Pharmacology  
 IT Diseases  
     chronic stable **angina pectoris: heart disease**  
     **Angina Pectoris (MeSH)**  
 IT Diseases  
     essential **hypertension: vascular disease**  
     **Hypertension (MeSH)**  
 IT Chemicals & Biochemicals  
     **mibefradil: antianginal-drug, antihypertensive-drug, T-channel**  
     **selective calcium antagonist**  
 ORGN Classifier  
     Hominidae 86215  
     Super Taxa  
         Primates; Mammalia; Vertebrata; Chordata; Animalia  
     Organism Name  
         human: patient  
     Taxa Notes  
         Animals, Chordates, Humans, Mammals, Primates, Vertebrates  
 RN 116644-53-2 (mibefradil)  
     7440-70-2 (**CALCIUM**)

L103 ANSWER 168 OF 198 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on  
 STN  
 ACCESSION NUMBER: 1997:376872 BIOSIS  
 DOCUMENT NUMBER: PREV199799676075  
 TITLE: Long -term anti-**anginal** and anti-**ischemic**  
     effects of **mibefradil**, the novel T-type  
     **calcium channel** blocker: A multicenter,  
     double-blind, placebo-controlled, randomized study vs  
     diltiazem SR.  
 AUTHOR(S): Caspi, Abraham [Reprint author]; Davies, Graham; Kobrin,  
     Isaac  
 CORPORATE SOURCE: Kaplan Hosp., Rehovot, Israel  
 SOURCE: Cardiovascular Drugs and Therapy, (1997) Vol. 11, No.  
     SUPPL. 2, pp. 335.  
     Meeting Info.: 7th International Symposium on  
     Cardiovascular Pharmacotherapy. Jerusalem, Israel. June  
     1-5, 1997.  
     ISSN: 0920-3206.  
 DOCUMENT TYPE: Conference; (Meeting)  
     Conference; Abstract; (Meeting Abstract)  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 4 Sep 1997  
     Last Updated on STN: 4 Sep 1997  
 ED Entered STN: 4 Sep 1997  
     Last Updated on STN: 4 Sep 1997  
 CC General biology - Symposia, transactions and proceedings 00520  
     Biochemistry studies - General 10060  
     **Cardiovascular system - Physiology and biochemistry 14504**  
     **Cardiovascular system - Heart pathology 14506**  
     **Cardiovascular system - Blood vessel pathology 14508**  
     Pharmacology - Clinical pharmacology 22005  
     Pharmacology - Cardiovascular system 22010  
 IT Major Concepts  
     Biochemistry and Molecular Biophysics; **Cardiovascular Medicine**  
     **(Human Medicine, Medical Sciences); Cardiovascular System**

(Transport and Circulation); Pharmacology  
 IT Chemicals & Biochemicals  
     MIBEFRADIL; **CALCIUM**; DILTIAZEM  
 IT Miscellaneous Descriptors  
     **ANTIANGINAL-DRUG**; BLOOD PRESSURE; **CARDIOVASCULAR**  
     **MEDICINE**; **CARDIOVASCULAR-DRUG**; DILTIAZEM SR;  
     **HEART DISEASE**; **HEART RATE**; **ISCHEMIA**;  
     MIBEFRADIL; PHARMACOLOGY; RATE-PRESSURE PRODUCT; **STABLE ANGINA**  
     PECTORIS; VASCULAR DISEASE  
 ORGN Classifier  
     Hominidae 86215  
     Super Taxa  
     Primates; Mammalia; Vertebrata; Chordata; Animalia  
     Organism Name  
     human  
     Taxa Notes  
     Animals, Chordates, Humans, Mammals, Primates, Vertebrates  
 RN 116644-53-2 (MIBEFRADIL)  
     7440-70-2 (**CALCIUM**)  
     42399-41-7 (DILTIAZEM)

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ACCESSION NUMBER: 1997:142528 BIOSIS  
 DOCUMENT NUMBER: PREV199799441731  
 TITLE: Block of **cardiac Ca-2+ channels**  
     by the new **Ca-2+** antagonist **Ro**  
     **40-5967**: Consequences on **heart**  
     rate and **cardiac** output.  
 AUTHOR(S): Mangoni, M.; Leuranguer, V.; Bourinet, E.; Nargeot, J.;  
     Richard, S.  
 CORPORATE SOURCE: CNRS ERS155, BP 5051, Montpellier, France  
 SOURCE: Biophysical Journal, (1997) Vol. 72, No. 2 PART 2, pp.  
     A256.  
     Meeting Info.: 41st Annual Meeting of the Biophysical  
     Society. New Orleans, Louisiana, USA. March 2-6, 1997.  
     CODEN: BIOJAU. ISSN: 0006-3495.  
 DOCUMENT TYPE: Conference; (Meeting)  
     Conference; Abstract; (Meeting Abstract)  
     Conference; (Meeting Poster)  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 2 Apr 1997  
     Last Updated on STN: 2 Apr 1997

ED Entered STN: 2 Apr 1997  
     Last Updated on STN: 2 Apr 1997  
 CC General biology - Symposia, transactions and proceedings 00520  
     Biochemistry studies - Minerals 10069  
     Biophysics - General 10502  
     **Cardiovascular system - General and methods 14501**  
     Pharmacology - General 22002  
 IT Major Concepts  
     Biochemistry and Molecular Biophysics; **Cardiovascular System**  
     **(Transport and Circulation)**; Pharmacology  
 IT Chemicals & Biochemicals  
     **RO 40-5967**; **CALCIUM**; MIBEFRADIL; NIFEDIPINE; DIHYDROPYRIDINE;  
     NICARDIPINE  
 IT Miscellaneous Descriptors  
     **ADULT**; **ANTIHYPERTENSIVE AGENT**; BIOCHEMISTRY AND BIOPHYSICS;  
     **CALCIUM**; **CALCIUM ANTAGONIST**; **CARDIAC ACTION**  
     **POTENTIAL**; **CARDIAC CHANNEL**; **CARDIAC OUTPUT**;

**CARDIOVASCULAR SYSTEM**; CIRCULATORY SYSTEM; DIHYDROPYRIDINE  
CLASS; **HEART RATE**; MIBEFRADIL; NEONATE; NICARDIPINE;  
NIFEDIPINE; RO 40-5967; VENTRICULAR MYOCYTE

## ORGN Classifier

Muridae 86375

## Super Taxa

Rodentia; Mammalia; Vertebrata; Chordata; Animalia

## Organism Name

rat

## Taxa Notes

Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,  
Rodents, Vertebrates

RN 116666-63-8 (RO 40-5967)

7440-70-2 (**CALCIUM**)

116644-53-2 (MIBEFRADIL)

21829-25-4 (NIFEDIPINE)

27790-75-6 (DIHYDROPYRIDINE)

55985-32-5 (NICARDIPINE)

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ACCESSION NUMBER: 1998:10212 BIOSIS

DOCUMENT NUMBER: PREV199800010212

TITLE: Rationale for the use of **calcium** antagonists in  
the treatment of silent myocardial **ischemia**.

AUTHOR(S): Cohn, Pete F. [Reprint author]

CORPORATE SOURCE: Cardiol. Div., Dep. Med., State Univ. New York Health Sci.  
Cent., T-17-020, Stony Brook, NY 11794-8171, USASOURCE: Clinical Therapeutics, (1997) Vol. 19, No. SUPPL. A, pp.  
74-91. print.

CODEN: CLTHDG. ISSN: 0149-2918.

DOCUMENT TYPE: Article

General Review; (Literature Review)

LANGUAGE: English

ENTRY DATE: Entered STN: 23 Dec 1997

Last Updated on STN: 23 Dec 1997

ED Entered STN: 23 Dec 1997

Last Updated on STN: 23 Dec 1997

AB Silent myocardial ischemia, whether it occurs at rest or during exercise, is associated with an unfavorable prognosis and may lead to sudden cardiac death. Agents used to treat silent myocardial ischemia have included nitrates, beta-blockers, and calcium antagonists (CAs). Despite treatment with traditional anti-ischemic agents, studies have shown that up to 40% of patients who receive what is considered to be clinically optimal antianginal therapy continue to have daily episodes of silent myocardial ischemia. The use of nitrates and beta-blockers is sometimes confounded by issues of tolerance and tolerability. Although the CAs have been found to be effective in decreasing the duration and frequency of episodes of silent ischemia, in general beta-blockers produce a greater reduction in these variables. Thus a need for effective and tolerable antiischemic agents persists. A new class of CAs, the tetralol derivatives, may show promise in this regard. The first of this new class, **mibefradil**, is characterized by selective blockade of T-type **calcium-ion channels** and has been shown in a few studies to reduce the frequency and duration of asymptomatic ischemic episodes in patients with stable exertional angina pectoris. Large-scale clinical trials are necessary before the efficacy and tolerability of this new CA can be compared fully with those of the beta-blockers and currently available CAs.

CC Pharmacology - General 22002



Pathology - Therapy 12512  
**Cardiovascular system - General and methods 14501**  
IT Major Concepts  
**Cardiovascular Medicine (Human Medicine, Medical Sciences);**  
Pharmacology  
IT Diseases  
**angina pectoris: heart disease, vascular disease**  
**Angina Pectoris (MeSH)**  
IT Diseases  
**silent myocardial ischemia: heart disease, vascular**  
**disease, treatment**  
**Myocardial Ischemia (MeSH)**  
IT Chemicals & Biochemicals  
**beta blockers: cardiovascular; calcium antagonist:**  
**cardiovascular; mibefradil: calcium channel blocker-drug,**  
**cardiovascular-drug, pharmacodynamics; nitrates:**  
**cardiovascular**  
ORGN Classifier  
Hominidae 86215  
Super Taxa  
Primates; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
human: patient  
Taxa Notes  
Animals, Chordates, Humans, Mammals, Primates, Vertebrates  
RN 116644-53-2 (mibefradil)  
14797-55-8 (nitrates)  
7440-70-2 (**CALCIUM**)

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ACCESSION NUMBER: 1998:2221 BIOSIS  
DOCUMENT NUMBER: PREV199800002221  
TITLE: Reappraisal of the importance of **heart rate** as a  
risk factor for **cardiovascular** morbidity and  
mortality.  
AUTHOR(S): Habib, Gabriel [Reprint author]  
CORPORATE SOURCE: Coronary Care Unit, VA Med. Cent., Sect. Cardiol., Rm  
3C-330D, 2002 Holcombe Blvd., Houston, TX 77030, USA  
SOURCE: Clinical Therapeutics, (1997) Vol. 19, No. SUPPL. A, pp.  
39-52. print.  
CODEN: CLTHDG. ISSN: 0149-2918.  
DOCUMENT TYPE: Article  
General Review; (Literature Review)  
LANGUAGE: English  
ENTRY DATE: Entered STN: 23 Dec 1997  
Last Updated on STN: 23 Dec 1997  
ED Entered STN: 23 Dec 1997  
Last Updated on STN: 23 Dec 1997  
AB Heart rate is a key determinant of myocardial oxygen consumption. Several  
lines of evidence support a consistent association between heart rate and  
cardiovascular mortality. Increments in heart rate are positively related  
to cardiovascular and sudden death in patients with hypertension or  
previous myocardial infarction and in the elderly with heart disease.  
This relationship is important because a number of commonly used  
cardiovascular agents, such as beta-blockers and calcium antagonists  
(CAs), can affect heart rate. Beta-blockers decrease heart rate and  
reduce morbidity and mortality in postmyocardial infarction patients. The  
CAs are a structurally diverse group of agents with different physiologic  
effects. The dihydropyridine CAs are not associated with a reduction in

heart rate. In fact, often they can cause reflex tachycardia as a result of potent systemic vasodilator action, which may provoke angina, especially in patients with ischemic heart disease. The nondihydropyridine CAs verapamil and diltiazem reduce heart rate but are associated with negative inotropy. **Mibefradil**, the first member of a new class of CAs, reduces heart rate and is not associated with negative inotropic effects. This unique pharmacologic profile may be of great value in treating hypertensive patients, particularly those with coexisting ischemic heart disease, and also patients with angina pectoris alone. However, the clinical benefit of pharmacologically reducing heart rate with **mibefradil** needs to be demonstrated in controlled trials.

CC **Cardiovascular system - General and methods** 14501  
 Pathology - Therapy 12512  
 Pharmacology - General 22002

IT Major Concepts  
**Cardiovascular Medicine (Human Medicine, Medical Sciences);**  
 Pharmacology

IT Diseases  
**angina pectoris: heart disease, vascular disease**  
**Angina Pectoris (MeSH)**

IT Diseases  
**heart disease: heart disease**  
**Heart Diseases (MeSH)**

IT Diseases  
**hypertension: vascular disease**  
**Hypertension (MeSH)**

IT Diseases  
 myocardial infarction: heart disease, vascular disease  
 Myocardial Infarction (MeSH)

IT Chemicals & Biochemicals  
**diltiazem: calcium channel blocker-drug, cardiovascular-drug;**  
**mibefradil: calcium channel blocker-drug, cardiovascular-drug;**  
**verapamil: calcium channel blocker-drug, cardiovascular-drug**

IT Miscellaneous Descriptors  
**cardiovascular morbidity; cardiovascular mortality;**  
**heart rate; myocardial oxygen consumption**

ORGN Classifier  
 Hominidae 86215  
 Super Taxa  
 Primates; Mammalia; Vertebrata; Chordata; Animalia  
 Organism Name  
 human: patient  
 Taxa Notes  
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 42399-41-7 (diltiazem)  
 116644-53-2 (mibefradil)  
 52-53-9 (verapamil)  
 7440-70-2 (**CALCIUM**)  
 7782-44-7 (OXYGEN)

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ACCESSION NUMBER: 1995:13186 BIOSIS  
 DOCUMENT NUMBER: PREV199598027486  
 TITLE: Effects of a new **calcium channel**  
 blocker **Ro 40-5967** in  
 patients with stable **angina pectoris**.  
 AUTHOR(S): Bakx, A. L. M.; Van Der Wall, E. E.; Braun, S.;  
 Emanuelsson, H.; Kobrin, I.; Bruschke, A. V. G.

CORPORATE SOURCE: Dep. Cardiol., Univ. Hosp., Leiden, Netherlands  
 SOURCE: European Heart Journal, (1994) Vol. 15, No. ABSTR. SUPPL.,  
 pp. 299.  
 Meeting Info.: Joint XIIth World Congress of Cardiology and  
 the XVIth Congress of the European Society of Cardiology.  
 Berlin, Germany. September 10-14, 1994.  
 CODEN: EHJODF. ISSN: 0195-668X.

DOCUMENT TYPE: Conference; (Meeting)  
 Conference; Abstract; (Meeting Abstract)  
 Conference; (Meeting Poster)

LANGUAGE: English

ENTRY DATE: Entered STN: 5 Jan 1995  
 Last Updated on STN: 5 Jan 1995

ED Entered STN: 5 Jan 1995  
 Last Updated on STN: 5 Jan 1995

CC General biology - Symposia, transactions and proceedings 00520  
 Biochemistry studies - General 10060  
 Pathology - Therapy 12512  
     **Cardiovascular system - Heart pathology 14506**  
     **Cardiovascular system - Blood vessel pathology 14508**  
 Pharmacology - Clinical pharmacology 22005  
 Pharmacology - Cardiovascular system 22010

IT Major Concepts  
     **Cardiovascular Medicine (Human Medicine, Medical Sciences);**  
     Pharmacology

IT Chemicals & Biochemicals  
     **CALCIUM**

IT Miscellaneous Descriptors  
     **CARDIOVASCULAR-DRUG; MEETING ABSTRACT; MEETING POSTER;**  
     RO-40-5967

ORGN Classifier  
     Hominidae 86215  
     Super Taxa  
         Primates; Mammalia; Vertebrata; Chordata; Animalia  
     Organism Name  
         human  
     Taxa Notes  
         Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 7440-70-2 (**CALCIUM**)

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ACCESSION NUMBER: 1997-0500012 PASCAL

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 reserved.

TITLE (IN ENGLISH): Safety of **mibefradil**, a new once-a-day,  
 selective T-type **calcium channel**  
 antagonist  
 Pharmacologic and clinical perspectives on  
**mibefradil: a new T-channel**  
 selective **calcium** antagonist

AUTHOR: KOBRIN I.; CHARLON V.; LINDBERG E.; PORDY R.  
 GILES Thomas D. (ed.)

CORPORATE SOURCE: Hoffmann-LaRoche, Nutley, New Jersey, United States  
 School of Medicine in New Orleans, Louisiana State  
 University Medical Center, New Orleans, Louisiana,  
 United States

SOURCE: The American journal of cardiology, (1997),  
 80(4B), 40C-46C, 18 refs.  
 ISSN: 0002-9149 CODEN: AJCDAG

DOCUMENT TYPE: Journal  
BIBLIOGRAPHIC LEVEL: Analytic  
COUNTRY: United States  
LANGUAGE: English  
AVAILABILITY: INIST-8674, 354000068013030060

UP 20001031

AB The safety and tolerability of **mibefradil**, a selective T-type **calcium channel** antagonist, were evaluated in 3,430 patients with essential hypertension and chronic stable angina pectoris treated in 15 double-blind placebo and active-controlled clinical trials and 2 open-label, long-term safety studies. Of these patients, 2,636 were treated with the recommended doses of mibefradil (50 and 100 mg) and form the basis of this report. With the 50-mg dose of mibefradil, the incidence of each adverse event was similar to, or lower than, that observed in the placebo-treated patients. Treatment with the 100-mg dose was associated with a slightly higher incidence compared to placebo of dizziness (2.1% vs 1.8%), leg edema (3.5% vs 1.4%), fatigue (2.1% vs 1.4%), and lightheadedness (2.1% vs 0.4%). The incidence of headache (4.6%) and angina pectoris (1.1%) was more frequent in patients treated with placebo. In active-controlled trials, a lower incidence of pedal edema (5.1%) was observed with mibefradil compared to amlodipine (25.7%), diltiazem SR/CD (9.4%), or nifedipine SR/GITS (17.4%). Overall, mibefradil was better tolerated than amlodipine and nifedipine SR/GITS and was as well tolerated as diltiazem SR/CD. Rates of premature discontinuation due to clinically adverse experiences with the 50- and 100-mg doses were 2.5% and 3.5%, respectively, compared with placebo (3.5%). No consistent pattern of laboratory adverse experiences were observed for **mibefradil**. Sinus bradycardia (**heart** rate <45 beats/minute) and first-degree atrioventricular block were the only relevant treatment-emergent **electrocardiographic** changes that occurred more frequently with **mibefradil** than with placebo. No evidence of first-dose effects was observed in mibefradil-treated patients, and withdrawal effects were not observed in clinical trials. There were no clinically important differences in safety profiles in the demographic subgroups for age, gender, or race. The results of this comprehensive safety analysis indicate that treatment with the recommended doses of mibefradil is well tolerated and safe.

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ACCESSION NUMBER: 1997-0484651 PASCAL  
COPYRIGHT NOTICE: Copyright .COPYRG. 1997 INIST-CNRS. All rights reserved.

TITLE (IN ENGLISH): **Mibefradil** in the treatment of chronic stable **angina** pectoris : Comparative studies with other **calcium** antagonists  
Pharmacologic and clinical perspectives on **mibefradil**: a new T-channel selective **calcium** antagonist

AUTHOR: DAVIES G. J.; TZIVONI D.; KOBRIN I.  
GILES Thomas D. (ed.)

CORPORATE SOURCE: Royal Postgraduate Medical School, Hammersmith Hospital, London, United Kingdom; Shaare Zedek Medical Center, Jerusalem, Israel; Hoffmann-LaRoche, Nutley, New Jersey, United States  
School of Medicine in New Orleans, Louisiana State University Medical Center, New Orleans, Louisiana, United States

SOURCE: The American journal of cardiology, (1997), 80(4B), 34C-39C, 21 refs.

ISSN: 0002-9149 CODEN: AJCDAG  
DOCUMENT TYPE: Journal  
BIBLIOGRAPHIC LEVEL: Analytic  
COUNTRY: United States  
LANGUAGE: English  
AVAILABILITY: INIST-8674, 354000068013030050  
UP 20001031

AB The ability of **mibefradil**, a new T-channel-selective **calcium** antagonist, to improve exercise tolerance and silent ischemic parameters in patients with chronic stable angina was compared in 3 separate trials with 2 other commonly used calcium antagonists: diltiazem SR (120 mg/twice daily) and amlodipine (10 mg/day). Compared with amlodipine, mibefradil 100 mg given once daily over a 3-week period resulted in a statistically significantly larger increase from baseline in total exercise tolerance test (ETT) duration (treatment difference of 40.9 sec,  $p = 0.04$ ), time to onset of angina (treatment difference 61.2 sec,  $p < 0.001$ ), and time to onset of ischemia (treatment difference of 54.4 sec,  $p = 0.004$ ). The decrease in weekly **anginal** episodes was 58% with **mibefradil** versus 19% with amlodipine, and the reduction in nitroglycerin consumption was 58% with mibefradil versus a 10% increase with amlodipine. The decrease in the number of silent ischemic episodes detected by a 48-hour Holter recording was significantly larger ( $p = 0.03$ ) with mibefradil 100 mg (88%) compared with amlodipine 10 mg (38%). Similarly, a larger decrease in the duration of silent **ischemia** was observed with **mibefradil** (69%) compared with that seen with amlodipine (38%). The preliminary results of a second trial comparing mibefradil with amlodipine were consistent with the first demonstrating that the improvement for all 3 ETT parameters was larger for **mibefradil** (ETT duration: 55.2 sec; delay in onset **angina**: 74.2 sec; time to onset of ischemia: 63.6 sec), but in this trial the treatment differences did not reach statistical significance. In the trial comparing mibefradil (100 mg once daily) with diltiazem SR (120 mg twice daily), both compounds had equivalent effects on all ETT parameters tested. Mibefradil produced a 21% increase in exercise duration compared with a 20% increase with diltiazem. Although **mibefradil** yielded larger increases in the time to onset of **angina** and the time to onset of 1-mm ST-segment depression (42% and 38%, respectively) than did diltiazem (34% and 25%, respectively), the treatment differences did not reach statistical significance. Both mibefradil and diltiazem SR were associated with at least a 70% reduction from baseline in **anginal** frequency and nitroglycerin consumption. **Mibefradil**-treated patients showed greater decreases in **heart** rate and the rate-pressure product at each stage of the ETT than patients treated with amlodipine or diltiazem SR. All 3 drugs were well tolerated. However, compared with mibefradil, amlodipine and diltiazem SR produced a higher incidence of leg edema. In conclusion, the effectiveness of mibefradil in improving all 3 ETT parameters was greater than that of amlodipine and equivalent to that of diltiazem SR. Moreover, **mibefradil** provided greater reductions in the **heart** rate and **cardiac** workload than did the other 2 drugs.

L103 ANSWER 175 OF 198 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED. on STN  
ACCESSION NUMBER: 1997-0484650 PASCAL  
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TITLE (IN ENGLISH): **Mibefradil** in the treatment of systemic **hypertension** : Comparative studies with other **calcium** antagonists

Pharmacologic and clinical perspectives on  
**mibefradil**: a new T-channel  
selective **calcium** antagonist

AUTHOR: MASSIE B. M.; LACOURCIERE Y.; VISKOPER R.; WOITTEZ  
A.; KOBRIN I.  
GILES Thomas D. (ed.)  
CORPORATE SOURCE: University of California, San Francisco, California,  
United States; Centre Hospitalier de Universite Laval,  
Quebec, Canada; Barzilai Medical Center, Askelon,  
Israel; Twenteborg Ziekenhuis, Almelo, Netherlands;  
Roche Laboratories, Nutley, New Jersey, United States  
School of Medicine in New Orleans, Louisiana State  
University Medical Center, New Orleans, Louisiana,  
United States  
SOURCE: The American journal of cardiology, (1997),  
80(4B), 27C-33C, 14 refs.  
ISSN: 0002-9149 CODEN: AJCDAG  
DOCUMENT TYPE: Journal  
BIBLIOGRAPHIC LEVEL: Analytic  
COUNTRY: United States  
LANGUAGE: English  
AVAILABILITY: INIST-8674, 354000068013030040

UP 20001031

AB This paper summarizes the results of 4 double-blind studies of  
**antihypertensive** therapy in which **mibefradil** was  
compared with other commonly used calcium antagonists (diltiazem CD,  
amlodipine, nifedipine SR, and nifedipine GITS) at the recommended dose  
range. A total of 640 patients were included, with 361 randomized to  
mibefradil, 98 to diltiazem CD, 119 to amlodipine, 71 to nifedipine SR,  
and 36 to nifedipine GITS. Trials included an active treatment phase of 6  
or 12 weeks in duration. Compared with diltiazem CD or nifedipine SR,  
mibefradil demonstrated statistically significant greater efficacy.  
Decreases in sitting diastolic blood pressure (SDBP) after treatment with  
mibefradil 100 mg once daily were  $14.0 \pm 7.8$  mm Hg compared with  $9.5$   
 $\pm 7.5$  mm Hg with diltiazem CD 360 mg once daily ( $p = 0.001$ ), and  $12.8$   
 $\pm 8.4$  mm Hg compared with  $8.1 \pm 19.2$  mm Hg with nifedipine SR 40 mg  
twice daily ( $p = 0.014$ ). Patients on mibefradil also had higher  
normalization (SDBP reduced to  $<90$  mm Hg) and response (SDBP reduction  
 $\geq 10$  mm Hg or normalization) rates than did those on diltiazem CD or  
nifedipine SR. The overall incidence of adverse events was similar among  
these 3 compounds, but the number of premature withdrawals due to adverse  
events was greater with both comparators than with mibefradil. Treatment  
with 100 mg mibefradil or 10 mg amlodipine once daily resulted in  
statistically significant decreases from baseline in SDBP of  $11.5 \pm$   
 $8.2$  mm Hg and  $13.2 \pm 7.9$  mm Hg, respectively, which were statistically  
equivalent. However, patients treated with amlodipine had a considerably  
greater incidence of leg edema than did those treated with mibefradil  
(33.6% vs 4.2%, respectively). Similarly, 100 mg mibefradil was  
equivalent in efficacy to 60 mg nifedipine GITS once daily, but patients  
on mibefradil experienced fewer vasodilatory related adverse events. In  
summary, mibefradil demonstrated superior efficacy to diltiazem CD and  
nifedipine SR and equivalent efficacy to amlodipine and nifedipine GITS  
in the treatment of hypertension.

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ACCESSION NUMBER: 1997-0484649 PASCAL  
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reserved.

TITLE (IN ENGLISH): **Antianginal and anti-ischemic**

effects of **mibefradil** in the treatment of patients with chronic stable **angina pectoris**  
Pharmacologic and clinical perspectives on **mibefradil: a new T-channel**

selective **calcium** antagonist

AUTHOR: ALPERT J. S.; BAKX A. L. M.; BRAUN S.; FRISHMAN W. H.; SCHNEEWEISS A.; TZIVONI D.; KOBRIN I. GILES Thomas D. (ed.)

CORPORATE SOURCE: University of Arizona Health Sciences Center, Tucson, Arizona, United States; University Hospital, Leiden, Netherlands; Tel Aviv Medical Center, Tel Aviv, Israel; Albert Einstein College of Medicine, Bronx, New York, United States; Shaare Zedek Medical Center, Jerusalem, Israel; Roche Laboratories, Nutley, New Jersey, United States  
School of Medicine in New Orleans, Louisiana State University Medical Center, New Orleans, Louisiana, United States

SOURCE: The American journal of cardiology, (1997), 80(4B), 20C-26C, 20 refs.

ISSN: 0002-9149 CODEN: AJCDAG

DOCUMENT TYPE: Journal

BIBLIOGRAPHIC LEVEL: Analytic

COUNTRY: United States

LANGUAGE: English

AVAILABILITY: INIST-8674, 354000068013030030

UP 20001031

AB Five placebo-controlled, double-blind, multicenter, parallel-design studies were performed to evaluate the antianginal and anti-ischemic characteristics of the novel T-channel-selective **calcium** antagonist, **mibefradil**, in the treatment of patients with chronic stable **angina pectoris**. Of the 5 studies, 2 were monotherapy dose-finding trials and 3 were conducted in patients receiving background antianginal therapy: either  $\beta$  blockers (2 studies) or long-acting nitrates (1 study). A total of 865 patients were randomized to 1 of 4 mibefradil dose groups (25, 50; 100, and 150 mg; n = 565) and placebo (n = 300). The antianginal and anti-ischemic effects of **mibefradil** were assessed across all 5 studies by evaluating exercise tolerance test variables, weekly number of anginal attacks and short-acting nitroglycerin consumption, and in both dose-finding studies, the number and total duration of silent ischemic episodes (48-hour Holter monitoring). A statistically significant increase in exercise duration was achieved in 3 of 5 studies with the 50-mg dose of mibefradil and in 3 of 3 studies with the 100-mg dose of the compound over the effects observed in the placebo groups. A significant delay in time to onset of ischemia during exercise was induced in all studies with the 50- and 100-mg doses of mibefradil. The 25-mg dose of mibefradil was not significantly better than placebo, and the effects of the 150-mg dose of the compound were similar to those observed with the 100-mg dose. Across all studies, a dose-related decrease was observed in the number of weekly anginal attacks and in weekly nitroglycerin consumption. Similarly, a significant dose-related decrease in the number and duration of silent ischemic episodes was observed during Holter monitoring for 48 hours in the 2 dose-finding studies. The antianginal and anti-ischemic effects were associated with a dose-related decrease in heart rate and double product both at rest and at exercise termination. Treatment with the 50- and 100-mg doses of mibefradil was found to be well tolerated and safe compared with placebo, a finding that held true for patients on chronic  $\beta$ -blocker or long-acting nitrate therapy. Taken together, these studies indicate that

mibefradil is an effective and well-tolerated once-daily treatment for chronic stable angina pectoris at doses of 50 and 100 mg, which are the lowest and highest effective doses of the compound, respectively.

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ACCESSION NUMBER: 1997-0484648 PASCAL

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TITLE (IN ENGLISH): **Antihypertensive effects of mibefradil in the treatment of mild-to-moderate systemic hypertension**  
Pharmacologic and clinical perspectives on **mibefradil: a new T-channel selective calcium antagonist**

AUTHOR: OPARIL S.; BERNINK P.; BURSZTYN M.; CARNEY S.; KOBRIN I.  
GILES Thomas D. (ed.)

CORPORATE SOURCE: University of Alabama at Birmingham, Birmingham, Alabama, United States; Martini Ziekenhuis, Groningen, Netherlands; Boston University Medical Center, Boston, Massachusetts, United States; John Hunter Hospital, New Castle, Australia; Hoffmann-LaRoche Laboratories, Nutley, New Jersey, United States  
School of Medicine in New Orleans, Louisiana State University Medical Center, New Orleans, Louisiana, United States

SOURCE: The American journal of cardiology, (1997), 80(4B), 12C-19C, 21 refs.  
ISSN: 0002-9149 CODEN: AJCDAG

DOCUMENT TYPE: Journal

BIBLIOGRAPHIC LEVEL: Analytic

COUNTRY: United States

LANGUAGE: English

AVAILABILITY: INIST-8674, 354000068013030020

UP 20001031

AB This report summarizes the results of 4 double-blind, placebo-controlled studies designed to determine the efficacy, tolerability, and dose-response characteristics of the novel T-channel-selective calcium antagonist, **mibefradil**, in the treatment of mild-to-moderate essential **hypertension**. Two of these studies were conducted in the general population of essential hypertensives, 1 in elderly patients, and 1 in patients on chronic hydrochlorothiazide treatment. A total of 1,116 patients were randomized to receive 1 of 7 doses of mibefradil (6.25-200 mg; n = 927), or placebo (n = 189). Each study demonstrated a significant linear dose response in the reduction of sitting diastolic (SDBP) and sitting systolic (SSBP) blood pressure. In all 4 trials, SDBP was significantly reduced with the recommended doses of 50 and 100 mg mibefradil (placebo-corrected treatment effects of -4.1 to -6.8 mm Hg and -8.8 to -11.1 mm Hg, respectively, for the 50- and 100-mg doses). A similar reduction in SSBP occurred in 3 of 4 studies at the 50-mg dose (-7.5 to -10.7 mm Hg) and in 4 of 4 studies at the 100-mg dose (-6.8 to -16.7 mm Hg). Lower doses did not reduce blood pressure significantly; doses > 100 mg had little additional effect and an increased incidence of adverse events. Overall, response and normalization rates were dose related and averaged 61% and 51%, respectively, for the 50-mg dose and 78% and 65%, respectively, for the 100-mg dose. The onset of the antihypertensive effect was gradual, with no first-dose effect; near maximal response was reached within 1-2 weeks. Trough/peak ratios ranged from 77-86% with the 50-mg dose and from



77-108% with the 100-mg dose, indicating a sustained effect over a 24-hour period. A slight decrease in heart rate was observed, ranging from -2.2 to -5.5 beats/min at the 50-mg dose and from -4.0 to -8.8 beats/min at the 100-mg dose. The efficacy and safety results were similar across all populations studied, including the elderly and hydrochlorothiazide-treated patients, indicating that no dose adjustment is needed for these populations. Thus, the results of these 4 placebo-controlled trials confirm that when taken at the recommended doses of 50 and 100 mg once daily, mibefradil is an effective, safe, and well-tolerated therapy for the treatment of mild-to-moderate hypertension.

L103 ANSWER 178 OF 198 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2001-44475 DRUGU P

TITLE: **Calcium channel** blockade limits transcriptional, translational and functional up-regulation of the **cardiac** calpain system after myocardial infarction.

AUTHOR: Sandmann S; Spormann J; Prenzel F; Shaw L; Schauer R

CORPORATE SOURCE: Univ.Kiel

LOCATION: Kiel, Ger.

SOURCE: J.Hypertens. (19, Suppl. 2, S92, 2001)

CODEN: JOHYD3 ISSN: 0263-6352

AVAIL. OF DOC.: Institute of Pharmacology, Christian-Albrechts- University of Kiel, Kiel, Germany.

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AB The effects of p.o. amlodipine, verapamil and **mibefradil** on the **cardiac** calpain system were investigated in rats after myocardial infarction. The results demonstrate that long-term **calcium channel** blockade with amlodipine and **mibefradil** prevents up-regulation of myocardial calpains causing a reduction of **cardiac** remodeling and limitation of infarct size. (conference abstract: 11th European Meeting on Hypertension, Milan, Italy, 2001).

L103 ANSWER 179 OF 198 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 1999-44237 DRUGU T S

TITLE: Combination of **calcium channel** blockers and beta blockers for exercise-induced **angina** pectoris.

AUTHOR: Cleophas T J; Van Der Vring J A; Zwinderman A H

LOCATION: Dordrecht; Leiden, Neth.

SOURCE: Cardiovasc.Drugs Ther. (13, No. 1, 17, 1999)

CODEN: CDTHET ISSN: 0920-3206

AVAIL. OF DOC.: Streekeziekenhuis, Zevenaar, Academic Hospital, Leiden, Netherlands.

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AB The aim of this double-blind parallel-group study was to compare the efficacy of amlodipine, diltiazem and **mibefradil** added to baseline beta blocker treatment in the prevention of **ischemia** in 335 patients with exercise-induced **angina**. All 3 drugs delayed onset of ST segment depression but **mibefradil** was the most effective. In conclusion, **calcium channel** blockers with negative chronotropic properties provide better delay of **ischemia** in patients with exercise-induced **angina**, but the concomitant

risk of intolerable dizziness largely reduces this benefit. (conference abstract: 8th International Symposium on Cardiovascular Pharmacotherapy, Amsterdam, The Netherlands, 1999).

L103 ANSWER 180 OF 198 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 1999-31421 DRUGU T S

TITLE: **Calcium channel** blockers added to beta blockers postpone exercise-induced myocardial ischaemia by reducing **heart** rate.

AUTHOR: Van Der Sluijs J P; Cleophas T J; Van Der Meulen J; Niemeyer M G; Zwinderman A H

CORPORATE SOURCE: Univ.Leiden

LOCATION: Dordrecht, Groningen; Leiden, Ger.

SOURCE: Neth.J.Med. (54, No. 5, A38, 1999)

CODEN: NJIEEQ ISSN: 0300-2977

AVAIL. OF DOC.: Merwede Hospital, Dordrecht, The Netherlands.

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AB The efficacy of the **calcium channel** blockers (CCB): amlodipine (AMD), diltiazem (DIL) and **mibefradil** (MIB) in preventing exercise-induced myocardial **ischemia** was compared in 335 patients on beta-blocker therapy in a 10 wk, double-blind, parallel-group trial. It was demonstrated that CCB with negative chronotropic property (DIL, MIB) provided a larger delay of ischemia in patients with exercise-induced angina pectoris than non-chronotropic CCB (AMD). However, the concomitant risk of intolerable dizziness may largely reduce this benefit. (conference abstract: Internist Meeting Veldhoven, The Netherlands, 1999).

L103 ANSWER 181 OF 198 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2000-24615 DRUGU P

TITLE: Effect of the **calcium channel** antagonist **mibefradil** on interstitial and perivascular fibrosis in myocardial infarction-induced **cardiac** failure in rats.

AUTHOR: Sandmann S; Bohle R M; Dreyer T; Unger T

CORPORATE SOURCE: Univ.Kiel; Univ.Giessen

LOCATION: Kiel; Giessen, Ger.

SOURCE: J.Hypertens. (17, Suppl. 3, S194, 1999)

CODEN: JOHYD3 ISSN: 0263-6352

AVAIL. OF DOC.: Institute of Pharmacology, University of Kiel, Germany.

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AB Chronic p.o. **Ro-40-5967 (mibefradil)** prevented coronary remodeling in rats with chronic MI-induced **heart**-failure. Such **cardioprotection** was greatest when this T-type calcium-antagonist (**Ro-40-5967**) was started before or just after onset of **ischemia**. (conference abstract: 9th European Meeting on Hypertension, Milan, Italy, 1999).

L103 ANSWER 182 OF 198 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2000-24722 DRUGU P

TITLE: The effects of the **calcium channel** antagonist **mibefradil** on intracellular Ca<sup>2+</sup>-homeostasis in myocardial infarction-induced **cardiac** failure in rats.

AUTHOR: Sandmann S; Min J Y; Meissner A; Unger T  
CORPORATE SOURCE: Univ.Kiel  
LOCATION: Kiel, Ger.  
SOURCE: J.Hypertens. (17, Suppl. 3, S280-S281, 1999)  
CODEN: JOHYD3 ISSN: 0263-6352  
AVAIL. OF DOC.: Institute of Pharmacology, University of Kiel, Kiel, Germany.  
LANGUAGE: English  
DOCUMENT TYPE: Journal  
FIELD AVAIL.: AB; LA; CT  
FILE SEGMENT: Literature

AB Effects of the preferentially T-channel blocking calcium channel antagonist, p.o. mibefradil (MBF), on hemodynamic parameters and intracellular calcium ((Ca<sup>2+</sup>)<sub>i</sub>)-handling and contractility of the left ventricular papillary muscle at different time points after MI were investigated in rats. MBF improved cardiac function of post-infarcted rats, lacking the negative inotropic effects of L-type Ca<sup>2+</sup> channel blockers. In addition, MBF protected the myocardium against (Ca<sup>2+</sup>)<sub>i</sub> overload after ischemia and increased beta-adrenergic responsiveness in chronically failing hearts. These effects of MBF point to a possible use of this compound in the therapy of heart failure. (conference abstract: 9th European Meeting on Hypertension, Milan, Italy, 1999).

L103 ANSWER 183 OF 198 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2000-24659 DRUGU P S

TITLE: Mibefradil, a calcium channel blocker, selective for T-type-Ca<sup>2+</sup>-channels. Acute cardiovascular effects and renal hemodynamics in conscious spontaneously hypertensive rats.

AUTHOR: Chung O; Kuhl H; Unger T  
CORPORATE SOURCE: Univ.Christian-Albrechts-Inst.Pharmacol.  
LOCATION: Kiel, Ger.  
SOURCE: J.Hypertens. (17, Suppl. 3, S223-S224, 1999) 1 Fig.  
CODEN: JOHYD3 ISSN: 0263-6352  
AVAIL. OF DOC.: Institute of Pharmacology, Christian-Albrechts University of Kiel, Germany.  
LANGUAGE: English  
DOCUMENT TYPE: Journal  
FIELD AVAIL.: AB; LA; CT  
FILE SEGMENT: Literature

AB The effects of i.v. mibefradil on systemic and renal hemodynamics in SHR were compared with those of nifedipine, verapamil and amlodipine, all i.v.. Unlike the other calcium channel blockers, mibefradil did not cause reflex tachycardia or reductions in renal blood flow (RBF). The results may be explained by the selective blockade of T-type Ca<sup>2+</sup> channels by mibefradil. (conference abstract: 9th European Meeting on Hypertension, Milan, Italy, 1999).

L103 ANSWER 184 OF 198 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 1998-42342 DRUGU T

TITLE: Subpopulation analysis of the combined hypertension trials of mibefradil, a selective T channel calcium antagonist.

AUTHOR: Pordy R  
CORPORATE SOURCE: Roche  
LOCATION: Nutley, N.J., USA  
SOURCE: J.Hypertens. (16, Suppl. 2, S231, 1998)  
CODEN: JOHYD3 ISSN: 0263-6352  
AVAIL. OF DOC.: Roche Laboratories, Nutley, NJ, U.S.A.

LANGUAGE: English  
DOCUMENT TYPE: Journal  
FIELD AVAIL.: AB; LA; CT  
FILE SEGMENT: Literature

AB Once-daily mibefradil (MB) treatment afforded better systolic B.P. control in females (vs. males), in the elderly (vs. adults), in blacks (vs. other races) and in nondiabetics (vs. diabetics) among 1561 hypertensive patients during several placebo- and active-controlled trials and a long-term open-label trial. However, MB therapy afforded better diastolic B.P. control in diabetics (vs. nondiabetics). Although this selective T-channel calcium antagonist (MB) lowered the B.P. in all subpopulations, it had the greatest effect in women and elderly patients. (conference abstract).

L103 ANSWER 185 OF 198 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 1998-04603 DRUGU P T S

TITLE: Focus on **mibefradil**: a novel selective T-type **calcium channel** blocker.

AUTHOR: Dunn A; Chow M S S

CORPORATE SOURCE: Univ.Connecticut

LOCATION: Storrs, Conn., USA

SOURCE: Formulary (32, No. 11, 1115-33, 1997) 1 Fig. 3 Tab. 22 Ref.

CODEN: FORMF ISSN: 1082-801X

AVAIL. OF DOC.: No Reprint Address.

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AB **Mibefradil** (MF) is reviewed. The chemistry, pharmacology, pharmacokinetics, clinical efficacy in **hypertension**, chronic stable angina pectoris, and CHF, adverse effects, formulary considerations, dosage and administration of MF are discussed. Clinical trials comparing MF and nifedipine (with or without lisinopril), amlodipine, diltiazem, enalapril or placebo are cited. Potential or known interactions with terfenadine, astemizole, cisapride, ciclosporin, quinidine, imipramine, desipramine, theophylline, warfarin, phenytoin, enalapril, metoprolol, and atenolol are outlined.

L103 ANSWER 186 OF 198 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 1998-09287 DRUGU P

TITLE: The T-**channel** selective **calcium** antagonist, **mibefradil**, markedly reduces hypoxia-induced myocyte death.

AUTHOR: Teerlink J R; Honbo N Y; Karliner J S

LOCATION: San Francisco, Cal., USA

SOURCE: Circulation (96, No. 8, Suppl. I, 742-43, 1997) 1 Fig.

CODEN: CIRCAZ ISSN: 0009-7322

AVAIL. OF DOC.: VA Medical Center, San Francisco, CA, U.S.A.

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AB The Authors assessed the ability of **mibefradil** to prevent **cardiac** myocyte death in a cell culture model of **ischemia**. In the hypoxic myocytes, **mibefradil** produced a dose-dependent reduction in cell death at each concentration. The results demonstrated that the T-**channel** selective **calcium** blocker, **mibefradil**, markedly reduces myocyte death in a culture model of **ischemia** and suggests that this agent may have benefits beyond reducing the frequency of anginal episodes. (conference abstract).

L103 ANSWER 187 OF 198 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 1997-24203 DRUGU P

TITLE: Comparison of the effect of the T-type **calcium-channel** antagonist **mibefradil** on contractile strength of the human myocardium with nifedipine and verapamil.

AUTHOR: Cremers B; Flesch M; Boehm M

CORPORATE SOURCE: Univ.Cologne

LOCATION: Cologne, Ger.

SOURCE: Z.Kardiol. (86, Suppl. 2, 270, 1997)

CODEN: ZKRDAX ISSN: 0300-5860

AVAIL. OF DOC.: Klinik III fuer Innere Medizin der Universitaet zu Cologne, Cologne, Germany.

LANGUAGE: German

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AB The negative inotropic effect of mibefradil was substantially less than the effects of nifedipine and verapamil in isolated strips of left ventricular papillary muscle from 18 patients with cardiac insufficiency. The ratio of the EC50 for this negative inotropic effect to the mean plasma concentration used therapeutically was much greater for mibefradil than for nifedipine or verapamil. Results indicate that **mibefradil** is likely to have a less pronounced **cardiosuppressive** effect than nifedipine or verapamil during treatment of arterial hypertension and stable angina pectoris. (conference abstract).

L103 ANSWER 188 OF 198 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 1997-43088 DRUGU P

TITLE: **Mibefradil**, a novel **calcium channel** antagonist, selectively protects against ventricular fibrillation induced by myocardial ischaemia.

AUTHOR: Billman G E

CORPORATE SOURCE: Univ.Ohio-State

LOCATION: Columbus, Ohio, USA

SOURCE: Eur.Heart J. (18, Abstr.Suppl., 164, 1997)

CODEN: EHJODF ISSN: 0195-668X

AVAIL. OF DOC.: Department of Physiology, The Ohio State University, Columbus, OH, U.S.A.

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AB Calcium channel antagonists can reduce calcium overload induced by myocardial **ischemia** and thereby protect against ventricular fibrillation (VF). **Mibefradil** selectively inhibits the **cardiac** calcium current in depolarized tissue without altering myocardial force development. Since cardiac tissue depolarizes during ischemia, this drug may be effective against **ischemia**-induced **arrhythmias**. The Authors set about to test this hypothesis. **Mibefradil** failed to prevent PES-induced **arrhythmias** during control conditions but prevented VF induced by either PES during **ischemia** or the exercise plus **ischemia** test conducted in dogs. **Mibefradil** may selectively prevent **ischemically**-induced VF without adverse actions on either A-V nodal conduction or contractile function. (conference abstract).

L103 ANSWER 189 OF 198 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 1997-41891 DRUGU T S  
TITLE: Safety of **mibefradil**, a new once-a-day, selective  
T-type **calcium channel** antagonist.  
AUTHOR: Kobrin I; Charlon V; Lindberg E; Pordy R  
CORPORATE SOURCE: Roche  
LOCATION: Nutley, N.J., USA  
SOURCE: Am.J.Cardiol. (80, No. 48, 40C-46C, 1997) 1 Fig. 9 Tab. 18  
Ref.  
CODEN: AJCDAG ISSN: 0002-9149  
AVAIL. OF DOC.: Hoffmann-La Roche, 340 Kingsland, Nutley, New Jersey 071 10-1  
99, U.S.A.  
LANGUAGE: English  
DOCUMENT TYPE: Journal  
FIELD AVAIL.: AB; LA; CT  
FILE SEGMENT: Literature  
AB The safety and tolerability of **mibefradil** (MB) were evaluated  
in 3430 patients with essential **hypertension** and chronic stable  
angina pectoris, treated in 15 double-blind, placebo-controlled trials  
and 2 open-label, long-term safety studies. Results showed that MB was  
generally well tolerated and safe at the recommended doses of 50-100  
mg/kg; the most common side-effects were leg edema and dizziness. Other  
drugs administered in this study included amlodipine, diltiazem and  
nifedipine.

L103 ANSWER 190 OF 198 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN  
ACCESSION NUMBER: 1998-04144 DRUGU P  
TITLE: Effects of the novel **calcium channel**  
blocker **mibefradil** on isolated working  
**hearts** of the rat. Comparison and interactions with  
amlodipin and gallopamil.  
AUTHOR: Matthes J; Antepohl W; Ruzsart R; Schroeder F; Twelker P;  
Wirth A; Herzig S  
CORPORATE SOURCE: Univ.Cologne  
LOCATION: Cologne, Ger.  
SOURCE: Arch.Pharmacol. (356, No. 4, Suppl. 1, R26, 1997) 1 Tab.  
CODEN: NSAPCC ISSN: 0028-1298  
AVAIL. OF DOC.: Dept. Pharmacology, Univ. Cologne, Gleueler Str. 24, 50931  
Koeln, Germany.  
LANGUAGE: English  
DOCUMENT TYPE: Journal  
FIELD AVAIL.: AB; LA; CT  
FILE SEGMENT: Literature  
AB The effects of **mibefradil** (MIB) on **cardiac**  
contractility and spontaneous beat frequency were compared with those of  
classical calcium channel blockers, amlodipine and gallopamil. In  
particular, it was determined whether, as reported for pairs of other  
calcium channel ligands, negative inotropism was more marked when MIB was  
combined with 1 of the other compounds. When MIB was given alone, no  
negative inotropic effects were seen, but the effects of amlodipine and  
gallopamil appeared at lower concentrations when MIB was present. The  
slight negative inotropic effect of MIB may be due to an interaction with  
T-type channels present in rat ventricle or the interaction with  
amlodipine and gallopamil may indicate allosteric interactions at L-type  
calcium channels. (conference abstract).

L103 ANSWER 191 OF 198 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN  
ACCESSION NUMBER: 1997-18788 DRUGU P  
TITLE: Comparative effects of the new T-type **calcium**  
**channel** antagonist **mibefradil** with  
nifedipine and verapamil on force of contraction in human

myocardium.  
AUTHOR: Cremers B; Flesch M; Boehm M  
CORPORATE SOURCE: Univ.Cologne  
LOCATION: Cologne, Ger.  
SOURCE: Arch.Pharmacol. (355, No. 4, Suppl., R72, 1997)  
CODEN: NSAPCC ISSN: 0028-1298  
AVAIL. OF DOC.: Klinik III Fuer Medizin der Universitat zu Cologne,  
Joseph-Strasse 9, D-50924, Cologne, Germany.  
LANGUAGE: English  
DOCUMENT TYPE: Journal  
FIELD AVAIL.: AB; LA; CT  
FILE SEGMENT: Literature  
AB **Mibefradil** (MIB) had only minor **cardiodepressive** effects in human myocardium in an in-vitro study using isolated and electrically stimulated left ventricular muscle preparations from 18 failing human hearts. Therefore, the use of MIB could be more advantageous than NIF and VER in the treatment of arterial hypertension and chronic stable angina pectoris especially in patients with decreased left ventricular function. Therapeutical applications of L-type calcium channel antagonists in the treatment of arterial hypertension and chronic stable angina pectoris are limited at least in part by the negative inotropic effects of these substances. These adverse effects could be detrimental in patients with decreased left ventricular function. (conference abstract).

L103 ANSWER 192 OF 198 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN  
ACCESSION NUMBER: 1996-48750 DRUGU P  
TITLE: Intravenous **mibefradil**, a T-typer **calcium channel** antagonist, improves **cardiac** hemodynamics in dogs with chronic **heart** failure: comparison with diltiazem and placebo.  
AUTHOR: Sabbah H N; Shimoyama H; Tanimura M; Shevlyagin S; Borzak S; Levine T B; Goldstein S  
CORPORATE SOURCE: Henry-Ford-Heart+Vasc.Inst.  
LOCATION: Detroit, Mich., USA  
SOURCE: Circulation (94, No. 8, Suppl., I556, 1996) 1 Tab.  
CODEN: CIRCAZ ISSN: 0009-7322  
AVAIL. OF DOC.: Henry Ford Heart and Vascular Institute, Detroit, MI, U.S.A.  
LANGUAGE: English  
DOCUMENT TYPE: Journal  
FIELD AVAIL.: AB; LA; CT  
FILE SEGMENT: Literature  
AB In a randomized, placebo-controlled comparative study of i.v. bolus and infused **mibefradil** and diltiazem in dogs, **mibefradil** improved **cardiac** hemodynamics in dogs with chronic **heart** failure whilst diltiazem affected only mean aortic pressure (MAP). The beneficial effects of **mibefradil** in **heart** failure compared to diltiazem may be a consequence of T-type calcium channel selectivity and its vasodilator effect free of negative inotropy. (conference abstract).

L103 ANSWER 193 OF 198 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN  
ACCESSION NUMBER: 1995-37690 DRUGU P  
TITLE: T,L-**calcium channel** blocker Ro 40-5967 maintains moderate negative inotropy both on normal and postischemic myocardium.  
AUTHOR: Simper D; Chambers D J  
CORPORATE SOURCE: Rayne-Inst.  
LOCATION: London, U.K.  
SOURCE: J.Mol.Cell.Cardiol. (27, No. 6, A250, 1995)

CODEN: JMCDAV ISSN: 0022-2828  
AVAIL. OF DOC.: Cardiac Surgical Research, Rayne Inst., St. Thomas' Hospital,  
London, England.

LANGUAGE: English  
DOCUMENT TYPE: Journal  
FIELD AVAIL.: AB; LA; CT  
FILE SEGMENT: Literature

AB The protective and negative inotropic effects of **Ro-40-5967** were evaluated in rat **hearts** subjected to 40 min global **ischemia** and 60 min reperfusion. In this model of extended **ischemia** and reperfusion, **Ro-40-5967** delayed **ischemic** contracture and did not depress ventricular function in **ischemically** injured and failing myocardium. In contrast to other calcium antagonists, **Ro-40-5967** may be more useful in the treatment of patients with chronic myocardial infarction and compromised LV function. (conference abstract).

L103 ANSWER 194 OF 198 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN  
ACCESSION NUMBER: 1993-30810 DRUGU P

TITLE: A New **Calcium Channel** Antagonist,  
**Ro 40-5967**, Limits Infarct Size  
in a Canine Model of **Ischemia** and Reperfusion.

AUTHOR: Heide R S van der; Jennings R B; Reimer K A  
LOCATION: Durham, North Carolina, United States  
SOURCE: J.Mol.Cell.Cardiol. (25, Suppl. 3, S17, 1993)  
CODEN: JMCDAV ISSN: 0022-2828

AVAIL. OF DOC.: Dept. of Pathology, Duke Univ. Med. Ctr., Durham, NC 27710,  
U.S.A.

LANGUAGE: English  
DOCUMENT TYPE: Journal  
FIELD AVAIL.: AB; LA; CT  
FILE SEGMENT: Literature

AB **RO-40-5967** and **ischemic** preconditioning (PC), but not verapamil (VER) (both i.v. infusion), limited the infarct size (IS) in a canine model of ischemia and reperfusion (REP). Transmural mean collateral blood flow (CBF) was the same in all groups. (congress abstract).

L103 ANSWER 195 OF 198 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN  
ACCESSION NUMBER: 1992-10365 DRUGU P S

TITLE: The Effect of **Ro-40 5967**, a  
Novel **Calcium Channel** Antagonist on  
Susceptibility to Ventricular Fibrillation.

AUTHOR: Billman G E  
LOCATION: Columbus, Ohio, United States  
SOURCE: Circulation (84, No. 4, Suppl. 2, 550, 1991)  
CODEN: CIRCAZ ISSN: 0009-7322

AVAIL. OF DOC.: The Ohio State University, Columbus, Ohio, U.S.A.

LANGUAGE: English  
DOCUMENT TYPE: Journal  
FIELD AVAIL.: AB; LA; CT  
FILE SEGMENT: Literature

AB The effects of i.v. **RO-40-5967** on susceptibility to ventricular fibrillation (VF) were investigated in dogs, and compared to verapamil (V) and diltiazem (D). Data indicate that **RO-40-5967** protects against VF without significant depression in **cardiac** contractile function or AV nodal conduction. (congress abstract).



L103 ANSWER 196 OF 198 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation  
on STN

ACCESSION NUMBER: 1998:729036 SCISEARCH  
THE GENUINE ARTICLE: 111MU  
TITLE: Subpopulation analysis of the combined  
**hypertension** trials of **mibefradil**, a  
selective T **channel calcium** antagonist  
AUTHOR: Pordy R  
CORPORATE SOURCE: Roche Labs, Nutley, NJ USA  
COUNTRY OF AUTHOR: USA  
SOURCE: JOURNAL OF HYPERTENSION, (JUN 1998) Vol. 16,  
Supp. [2], pp. S231-S231. MA P31005.  
ISSN: 0263-6352.  
PUBLISHER: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST,  
PHILADELPHIA, PA 19106-3621 USA.  
DOCUMENT TYPE: Conference; Journal  
LANGUAGE: English  
REFERENCE COUNT: 0  
ENTRY DATE: Entered STN: 1998  
Last Updated on STN: 1998  
ED Entered STN: 1998  
Last Updated on STN: 1998

L103 ANSWER 197 OF 198 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation  
on STN

ACCESSION NUMBER: 1998:765730 SCISEARCH  
THE GENUINE ARTICLE: 125NL  
TITLE: Chronic T-type **calcium channel**  
blockade with **mibefradil** in hyperinsulinemic,  
insulin-resistant and **hypertensive** rats (vol 34,  
pg 121, 1997)  
AUTHOR: Verma S; Bhanot S; Hicke A; McNeill J H (Reprint)  
CORPORATE SOURCE: Univ British Columbia, Fac Pharmaceut Sci, Vancouver, BC  
V6T 1Z3, Canada (Reprint)  
COUNTRY OF AUTHOR: Canada  
SOURCE: CARDIOVASCULAR RESEARCH, (OCT 1998) Vol. 40, No.  
1, pp. 230-230.  
ISSN: 0008-6363.  
PUBLISHER: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM,  
NETHERLANDS.  
DOCUMENT TYPE: Errata; Journal  
LANGUAGE: English  
REFERENCE COUNT: 1  
ENTRY DATE: Entered STN: 1998  
Last Updated on STN: 1998  
ED Entered STN: 1998  
Last Updated on STN: 1998

L103 ANSWER 198 OF 198 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation  
on STN

ACCESSION NUMBER: 1996:741883 SCISEARCH  
THE GENUINE ARTICLE: VL701  
TITLE: The effects of **mibefradil**, a novel  
**calcium channel** antagonist on  
ventricular **arrhythmias** induced by myocardial  
**ischemia** and programmed electrical stimulation  
(Vol 277, pg 1517, 1996)  
AUTHOR: Billman G E (Reprint); Hamlin R L  
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (  
OCT 1996) Vol. 279, No. 1, pp. 442-442.

ISSN: 0022-3565.  
PUBLISHER: WILLIAMS & WILKINS, 351 WEST CAMDEN ST, BALTIMORE, MD  
21201-2436.  
DOCUMENT TYPE: Errata; Journal  
FILE SEGMENT: LIFE  
LANGUAGE: English  
REFERENCE COUNT: 1  
ENTRY DATE: Entered STN: 1996  
Last Updated on STN: 1996  
ED Entered STN: 1996  
Last Updated on STN: 1996

=&gt; d his l102

(FILE 'HCAPLUS, MEDLINE, BIOSIS, PASCAL, JICST-EPLUS, EMBASE, CANCERLIT,  
 DRUGU, SCISEARCH, WPIX, CONF, CONFSCI' ENTERED AT 14:00:10 ON 14 JUL 2005)  
 L102 2 DUP REM L101 (1 DUPLICATE REMOVED)

=&gt; d que l102

L23 QUE ABB=ON PLU=ON (CA OR ?CALCIUM?) (2A) (?CHANNEL? OR ?  
 SIGNAL?)  
 L91 196 SEA DRUZGALA, P?/AU  
 L92 1696 SEA MILNER, P?/AU  
 L93 1153 SEA PFISTER, J?/AU  
 L94 82454 SEA ZHANG, X?/AU  
 L95 490 SEA (L91 OR L92 OR L93 OR L94) AND L23  
 L96 3 SEA L95 AND (?MIBEFRADIL? OR ?POSICOR? OR (RO(1W) 40(1W)  
 5967))  
 L97 3 SEA L95 AND ARYX/CS,SO,PA  
 L98 3 SEA (L96 OR L97)  
 L99 2 DUP REM L98 (1 DUPLICATE REMOVED)  
 L100 3 SEA (L91 OR L92 OR L93 OR L94) AND (?MIBEFRADIL? OR ?POSICOR?  
 OR (RO(1W) 40(1W) 5967))  
 L101 3 SEA L99 OR L100  
 L102 2 DUP REM L101 (1 DUPLICATE REMOVED)

=&gt; d ibib ed ab l102

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, BIOSIS' - CONTINUE? (Y)/N:y

L102 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2003:301058 HCAPLUS

DOCUMENT NUMBER: 138:297661

TITLE: **Mibefradil-based compounds as  
 calcium channel blockers useful in  
 the treatment of hypertension and angina**

INVENTOR(S): **Druzgala, Pascal; Milner, Peter G.  
 ; Pfister, Jurg R.; Zhang, Xiaoming**

PATENT ASSIGNEE(S): **Aryx Therapeutics, USA**

SOURCE: PCT Int. Appl., 50 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003031415	A1	20030417	WO 2002-US32562	20021010
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

CA 2462913	AA	20030417	CA 2002-2462913	20021010
US 2003130330	A1	20030710	US 2002-269139	20021010
US 6608097	B2	20030819		
EP 1438297	A1	20040721	EP 2002-773743	20021010
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2005508949	T2	20050407	JP 2003-534399	20021010
US 2004034237	A1	20040219	US 2003-643699	20030818
PRIORITY APPLN. INFO.:			US 2001-328588P	P 20011010
			US 2002-269139	A1 20021010
			WO 2002-US32562	W 20021010

OTHER SOURCE(S): MARPAT 138:297661

ED Entered STN: 18 Apr 2003

AB The invention provides **mibefradil**-based **calcium channel** blockers I [X = bond, (CH<sub>2</sub>)<sub>n</sub>, O, S, O(CH<sub>2</sub>)<sub>n</sub> (n = 1-6); R<sub>1</sub> = C1-6 alkyl, optionally substituted with OH or NH<sub>2</sub>; R<sub>2</sub> = F, COOR<sub>5</sub> (R<sub>5</sub> = R<sub>1</sub>); R<sub>3</sub> = CH<sub>3</sub>, (CH<sub>2</sub>)<sub>n</sub>COOR<sub>6</sub>, (n = 1-6; R<sub>6</sub> = R<sub>1</sub>); R<sub>4</sub> = (CH<sub>2</sub>)<sub>n</sub>COR<sub>7</sub>R<sub>8</sub>, (CH<sub>2</sub>)<sub>n</sub>R<sub>10</sub>R<sub>11</sub>, Q<sub>1</sub>; R<sub>7</sub> = O, NH, NR<sub>9</sub>, R<sub>8</sub> = optionally substituted aryl or heterocyclyl; R<sub>9</sub> = C1-6 alkyl; R<sub>10</sub> = O, S, SO, SO<sub>2</sub>, NH, NR<sub>12</sub>, N(CH<sub>2</sub>)<sub>m</sub>COOR<sub>13</sub>; R<sub>11</sub> = aryl or heterocyclyl optionally substituted with (CH<sub>2</sub>)<sub>n</sub>COOR<sub>14</sub>, R<sub>12</sub>-R<sub>14</sub> = R<sub>1</sub>; R<sub>15</sub> = (CH<sub>2</sub>)<sub>n</sub> COOR<sub>16</sub>, R<sub>16</sub> = R<sub>1</sub>; R<sub>17</sub> = absent or COOR<sub>18</sub>; R<sub>18</sub> = R<sub>1</sub>; n = 1-6] useful in the treatment of hypertension, angina pectoris, ischemia, arrhythmias and cardiac insufficiency.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=&gt; d ibib ed ab l102 2

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, BIOSIS' - CONTINUE? (Y)/N:y

L102 ANSWER 2 OF 2 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN  
ACCESSION NUMBER: 2003:422097 BIOSIS  
DOCUMENT NUMBER: PREV200300422097  
TITLE: Materials and methods for the treatment of hypertension and angina.  
AUTHOR(S): **Druzgala, Pascal** [Inventor, Reprint Author];  
**Milner, Peter G.** [Inventor]; **Pfister, Jurg**  
[Inventor]; **Zhang, Xiaoming** [Inventor]  
CORPORATE SOURCE: ASSIGNEE: **ARYx** Therapeutics, Santa Clara, CA, USA  
PATENT INFORMATION: US 6608097 20030819  
SOURCE: Official Gazette of the United States Patent and Trademark  
Office Patents, (Aug 19 2003) Vol. 1273, No. 3.  
<http://www.uspto.gov/web/menu/patdata.html>. e-file.  
ISSN: 0098-1133 (ISSN print).  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
ENTRY DATE: Entered STN: 10 Sep 2003  
Last Updated on STN: 10 Sep 2003

ED Entered STN: 10 Sep 2003

Last Updated on STN: 10 Sep 2003

AB The subject invention provides useful and novel **calcium channel** blockers based upon **mibefradil**. The subject invention also provides methods for synthesizing the compounds of the invention. The invention also provides methods for the control or prevention of hypertension, angina pectoris, ischemia, arrhythmias, and cardiac insufficiency in a patient by administering a compound, or composition, of the invention to an individual in need of such treatment.

=> file stnguide

FILE 'STNGUIDE' ENTERED AT 14:23:18 ON 14 JUL 2005

USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT

COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE

AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.

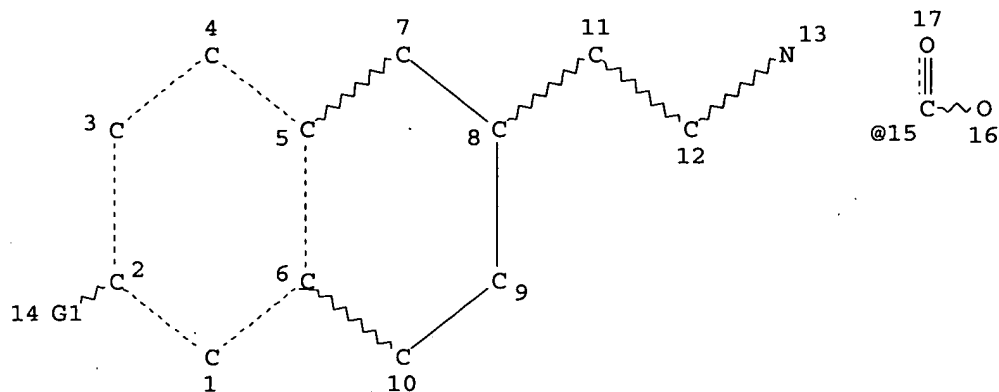
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4/4

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DEFAULT ECLEVEL IS LIMITED

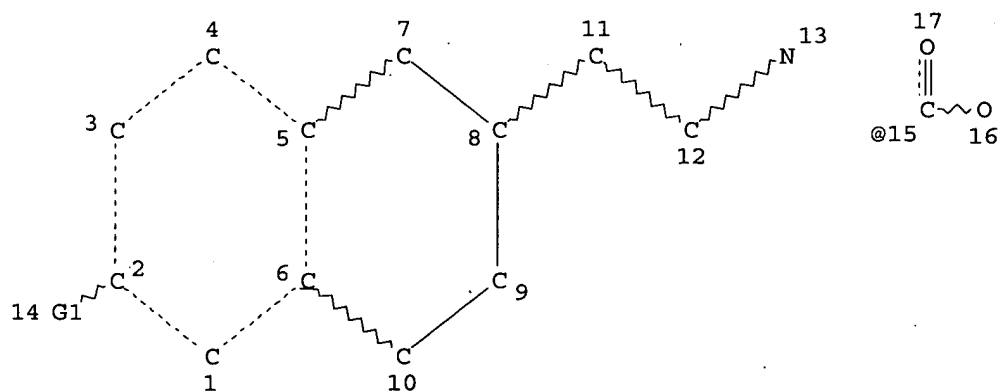
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STEREO ATTRIBUTES: NONE  
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312 ANSWERS

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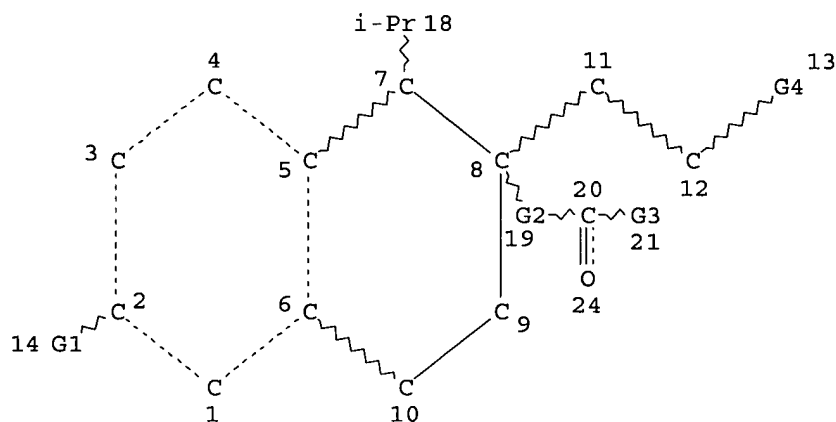
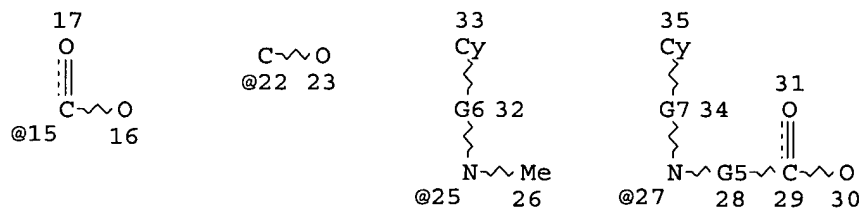
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NUMBER OF NODES IS 17

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L8 312 SEA FILE=REGISTRY SSS FUL L6  
L13 STR



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REP G2=(0-8) A  
VAR G3=O/22  
VAR G4=25/27  
REP G5=(1-6) C  
REP G6=(1-10) A  
REP G7=(1-10) A  
NODE ATTRIBUTES:  
CONNECT IS E4 RC AT 8  
DEFAULT MLEVEL IS ATOM  
GGCAT IS UNS AT 33  
GGCAT IS UNS AT 35  
DEFAULT ECLEVEL IS LIMITED

## GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED  
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## STEREO ATTRIBUTES: NONE

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135 ANSWERS



=&gt; d que nos 141

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L6      STR
L8      312 SEA FILE=REGISTRY SSS FUL L6
L13     STR
L15     135 SEA FILE=REGISTRY SUB=L8 SSS FUL L13
L16     1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND L4
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L25     136 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15 (L) L23
L27     134 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 NOT L16
L28     69 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L27
L29     7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  116644-53-2D?
L30     76 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L28 OR L29
L31     21 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L30 (L) L23
L35     QUE ABB=ON  PLU=ON  ?HYPERTENS? OR ?ANGINA? OR ?ISCHEM?
      OR ?ARRHYTHM? OR ?CARDIAC? OR ?CARDIO? OR HEART
L38     152 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15 (L) L35
L39     47 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25 AND L38
L40     59 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L31 OR L39
L41     53 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L40 AND (AY<2002 OR PY<2002
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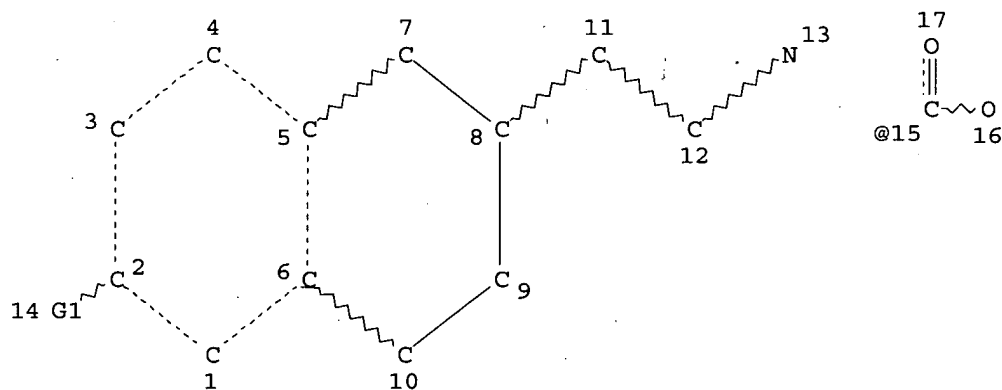
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L6 STR



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NODE ATTRIBUTES:

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DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

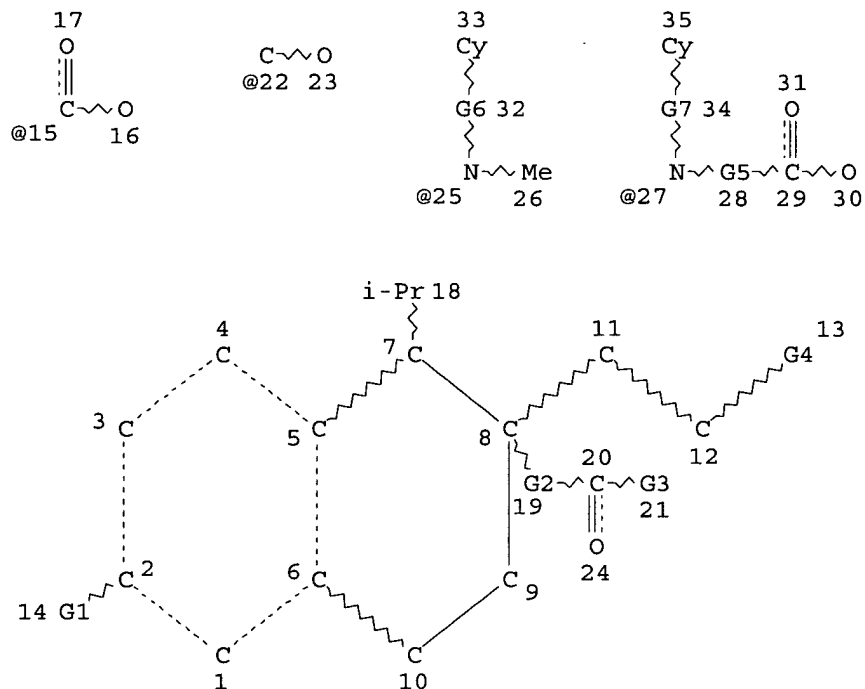
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NUMBER OF NODES IS 17

STEREO ATTRIBUTES: NONE

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L13 STR



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VAR G3=O/22  
VAR G4=25/27  
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REP G6=(1-10) A  
REP G7=(1-10) A  
NODE ATTRIBUTES:  
CONNECT IS E4 RC AT 8  
DEFAULT MLEVEL IS ATOM  
GGCAT IS UNS AT 33  
GGCAT IS UNS AT 35  
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
RING(S) ARE ISOLATED OR EMBEDDED  
NUMBER OF NODES IS 35

STEREO ATTRIBUTES: NONE

L15 135 SEA FILE=REGISTRY SUB=L8 SSS FUL L13  
L23 QUE ABB=ON PLU=ON (CA OR ?CALCIUM?) (2A) (?CHANNEL? OR ?  
SIGNAL?)  
L35 QUE ABB=ON PLU=ON ?HYPERTENS? OR ?ANGINA? OR ?ISCHEM?  
OR ?ARRHYTHM? OR ?CARDIAC? OR ?CARDIO? OR HEART  
L42 58 SEA L15  
L44 38 SEA L42 AND (L23/IT,ST,CC OR L35/IT,ST,CC)  
L45 33 SEA L44 AND (AY<2002 OR PY<2002 OR PRY<2002)

=> d que 190

L84 43 SEA FILE=WPIX ABB=ON PLU=ON (MIBEFRAIDIL/BIX OR POSICOR/BIX

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OR RO-40-5967/BIX)
L85      16553 SEA FILE=WPIX ABB=ON PLU=ON A61P009?/IPC
L86      44034 SEA FILE=WPIX ABB=ON PLU=ON (B14-F01? OR C14-F01? OR
          B14-F02? OR C14-F02?)/MC
L87      30 SEA FILE=WPIX ABB=ON PLU=ON L84 AND (L85 OR L86)
L88      18 SEA FILE=WPIX ABB=ON PLU=ON L87 AND ((CA/BIX OR ?CALCIUM?/BIX
          )(2A)(?CHANNEL?/BIX OR ?SIGNAL?/BIX))
L89      17 SEA FILE=WPIX ABB=ON PLU=ON L87 AND (AY<2002 OR PY<2002 OR
          PRY<2002)
L90      9 SEA FILE=WPIX ABB=ON PLU=ON L88 AND L89

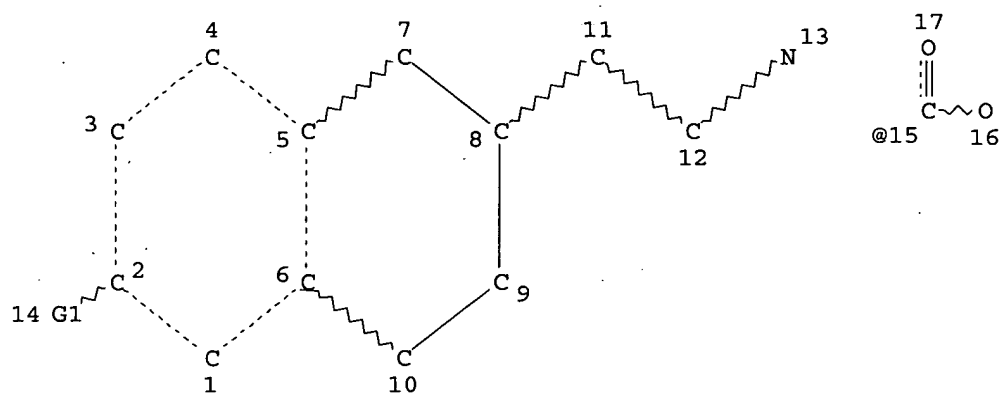
```

=> d que 152

```

L1      1 SEA FILE=HCAPLUS ABB=ON PLU=ON US2003-643699/APPS
L3      TRANSFER PLU=ON L1 1- RN :      3 TERMS
L4      3 SEA FILE=REGISTRY ABB=ON PLU=ON L3
L6      STR

```



```

VAR G1=X/15
NODE ATTRIBUTES:
CONNECT IS E4 RC AT 8
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

```

```

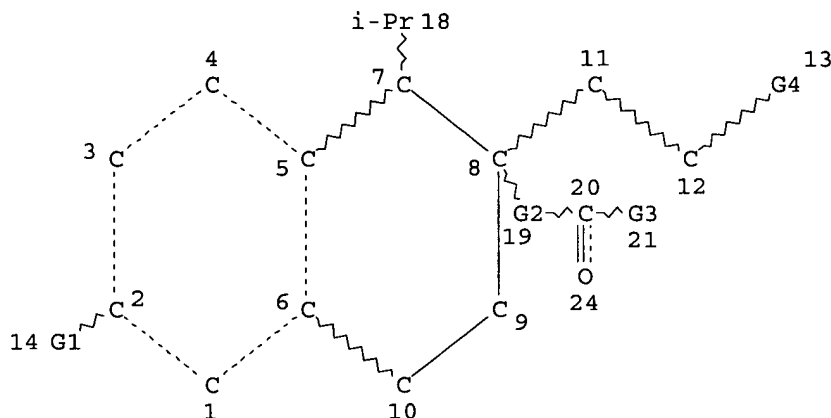
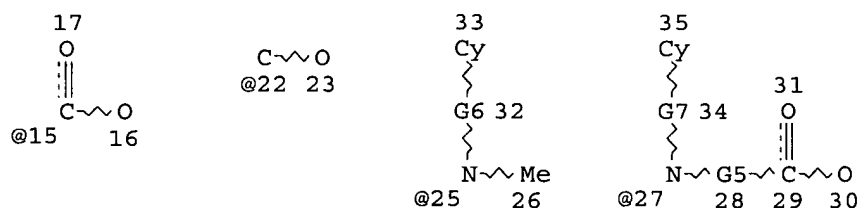
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 17

```

```

STEREO ATTRIBUTES: NONE
L8      312 SEA FILE=REGISTRY SSS FUL L6
L13     STR

```



```

VAR G1=X/15
REP G2=(0-8) A
VAR G3=O/22
VAR G4=25/27
REP G5=(1-6) C
REP G6=(1-10) A
REP G7=(1-10) A
NODE ATTRIBUTES:
CONNECT IS E4 RC AT 8
DEFAULT MLEVEL IS ATOM
GGCAT IS UNS AT 33
GGCAT IS UNS AT 35
DEFAULT ECLEVEL IS LIMITED

```

```

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 35

```

```

STEREO ATTRIBUTES: NONE

```

```

L15      135 SEA FILE=REGISTRY SUB=L8 SSS FUL L13
L16      1 SEA FILE=REGISTRY ABB=ON PLU=ON L15 AND L4
L23      QUE ABB=ON PLU=ON (CA OR ?CALCIUM?) (2A) (?CHANNEL? OR ?
          SIGNAL?)
L27      134 SEA FILE=REGISTRY ABB=ON PLU=ON L15 NOT L16
L35      QUE ABB=ON PLU=ON ?HYPERTENS? OR ?ANGINA? OR ?ISCHEM?
          OR ?ARRHYTHM? OR ?CARDIAC? OR ?CARDIO? OR HEART
L46      326 SEA FILE=TOXCENTER ABB=ON PLU=ON L15
L47      229 SEA FILE=TOXCENTER ABB=ON PLU=ON L46 AND L23
L48      164 SEA FILE=TOXCENTER ABB=ON PLU=ON L47 AND L35
L49      12 SEA FILE=TOXCENTER ABB=ON PLU=ON L48 AND REVIEW/DT
L50      36 SEA FILE=TOXCENTER ABB=ON PLU=ON L27
L51      35 SEA FILE=TOXCENTER ABB=ON PLU=ON L50 AND (PY<2002 OR

```

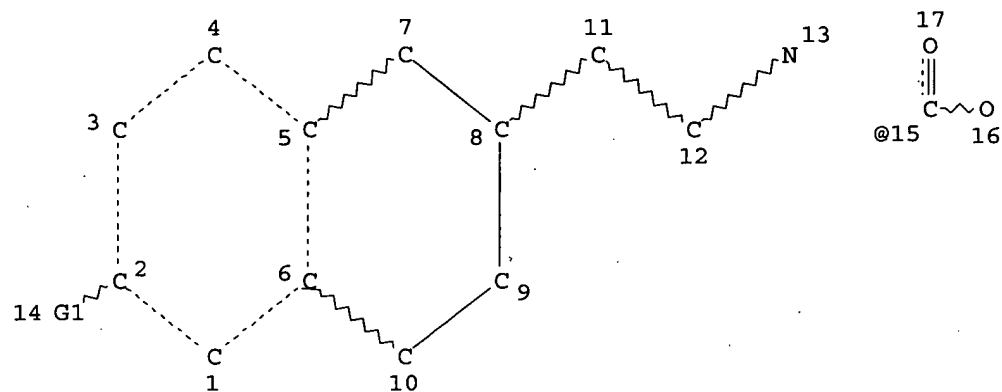
MY&lt;2002)

L52 47 SEA FILE=TOXCENTER ABB=ON PLU=ON L49 OR L51

=&gt; d que 182

L6

STR



VAR G1=X/15

NODE ATTRIBUTES:

CONNECT IS E4 RC AT 8

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

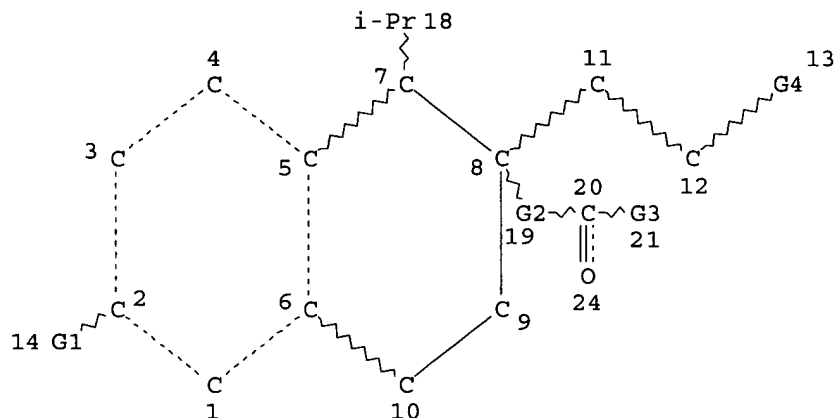
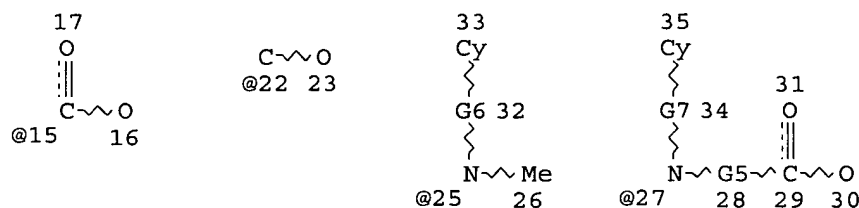
RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 17

STEREO ATTRIBUTES: NONE

L8 312 SEA FILE=REGISTRY SSS FUL L6

L13 STR



```

VAR G1=X/15
REP G2=(0-8) A
VAR G3=O/22
VAR G4=25/27
REP G5=(1-6) C
REP G6=(1-10) A
REP G7=(1-10) A
NODE ATTRIBUTES:
CONNECT IS E4 RC AT 8
DEFAULT MLEVEL IS ATOM
GGCAT IS UNS AT 33
GGCAT IS UNS AT 35
DEFAULT ECLEVEL IS LIMITED

```

```

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 35

```

```

STEREO ATTRIBUTES: NONE

```

```

L15      135 SEA FILE=REGISTRY SUB=L8 SSS FUL L13
L23      QUE ABB=ON PLU=ON (CA OR ?CALCIUM?) (2A) (?CHANNEL? OR ?
          SIGNAL?)
L68      SEL ABB=ON PLU=ON L15 1- CHEM :      154 TERMS
L69      935 SEA FILE=EMBASE ABB=ON PLU=ON L68
L70      511 SEA FILE=EMBASE ABB=ON PLU=ON L69 AND L23
L77      47 SEA FILE=EMBASE ABB=ON PLU=ON L70 AND ((CA/CT OR ?CALCIUM?/CT
          ) (2A) (?CHANNEL?/CT OR ?SIGNAL?/CT))
L79      39 SEA FILE=EMBASE ABB=ON PLU=ON L77/MAJ
L80      24 SEA FILE=EMBASE ABB=ON PLU=ON L79 AND (PY<2002 OR MY<2002)
L82      6 SEA FILE=EMBASE ABB=ON PLU=ON L80 AND (?HYPERTENS?/CT OR
          ?ANGINA?/CT OR ?ISCHEM?/CT OR ?ARRHYTHM?/CT OR ?CARDIAC?/CT OR
          ?CARDIO?/CT OR HEART/CT)

```

=> d his 167

(FILE 'MEDLINE, BIOSIS, PASCAL, JICST-EPLUS, CANCERLIT, DRUGU, SCISEARCH'  
ENTERED AT 13:01:21 ON 14 JUL 2005)

L67 83 S L65 AND (?HYPERTENS? OR ?ANGINA? OR ?ISCHEM? OR ?ARRHYTH? OR

=> d que nos 167

L6 STR  
L8 312 SEA FILE=REGISTRY SSS FUL L6  
L13 STR  
L15 135 SEA FILE=REGISTRY SUB=L8 SSS FUL L13  
L23 QUE ABB=ON PLU=ON (CA OR ?CALCIUM?) (2A) (?CHANNEL? OR ?  
SIGNAL?)  
L35 QUE ABB=ON PLU=ON ?HYPERTENS? OR ?ANGINA? OR ?ISCHEM?  
OR ?ARRHYTHM? OR ?CARDIAC? OR ?CARDIO? OR HEART  
L54 SEL PLU=ON L15 1- CHEM : 154 TERMS  
L55 2569 SEA L54  
L57 925 SEA L55 (10A) L23  
L59 981 SEA L55 (10A) L35  
L60 483 SEA L57 AND L59  
L61 269 DUP REM L60 (214 DUPLICATES REMOVED)  
L62 229 SEA L61 AND L23/IT,ST,CT,CC,TI  
L63 246 SEA L61 AND L35/IT,ST,CT,CC,TI  
L64 211 SEA L62 AND L63  
L65 142 SEA L64 AND (AY<2002 OR PY<2002 OR PRY<2002 OR MY<2002)  
L67 83 SEA L65 AND (?HYPERTENS? OR ?ANGINA? OR ?ISCHEM? OR ?ARRHYTH?  
OR ?ANTIHYPERTENS? OR ?ANTIANGINA? OR ?ANTIISCHEM? OR ?ANTIARRH  
YTHM?)/IT,ST,CC,CT,TI

=> d his 1102

(FILE 'HCAPLUS, MEDLINE, BIOSIS, PASCAL, JICST-EPLUS, EMBASE, CANCERLIT,  
DRUGU, SCISEARCH, WPIX, CONF, CONFSCI' ENTERED AT 14:00:10 ON 14 JUL 2005)

L102 2 DUP REM L101 (1 DUPLICATE REMOVED)

=> d que 1102

L23 QUE ABB=ON PLU=ON (CA OR ?CALCIUM?) (2A) (?CHANNEL? OR ?  
SIGNAL?)  
L91 196 SEA DRUZGALA, P?/AU  
L92 1696 SEA MILNER, P?/AU  
L93 1153 SEA PFISTER, J?/AU  
L94 82454 SEA ZHANG, X?/AU  
L95 490 SEA (L91 OR L92 OR L93 OR L94) AND L23  
L96 3 SEA L95 AND (?MIBEFRADIL? OR ?POSICOR? OR (RO(1W) 40(1W)  
5967))  
L97 3 SEA L95 AND ARYX/CS,SO,PA  
L98 3 SEA (L96 OR L97)  
L99 2 DUP REM L98 (1 DUPLICATE REMOVED)  
L100 3 SEA (L91 OR L92 OR L93 OR L94) AND (?MIBEFRADIL? OR ?POSICOR?  
OR (RO(1W) 40(1W) 5967))  
L101 3 SEA L99 OR L100  
L102 2 DUP REM L101 (1 DUPLICATE REMOVED)

=> d his ful

(FILE 'HOME' ENTERED AT 11:01:38 ON 14 JUL 2005)

FILE 'STNGUIDE' ENTERED AT 11:01:46 ON 14 JUL 2005

L1 FILE 'HCAPLUS' ENTERED AT 11:02:45 ON 14 JUL 2005  
1 SEA ABB=ON PLU=ON US2003-643699/APPS  
SAVE TEMP L1 KAN699HCAAPP/A  
D IALL

FILE 'STNGUIDE' ENTERED AT 11:03:21 ON 14 JUL 2005

L2 FILE 'WPIX' ENTERED AT 11:04:32 ON 14 JUL 2005  
1 SEA ABB=ON PLU=ON US2003-643699/APPS  
SAVE TEMP L2 KAN699WPIAPP/A  
D IALL CMC

FILE 'STNGUIDE' ENTERED AT 11:05:04 ON 14 JUL 2005

FILE 'REGISTRY' ENTERED AT 11:06:05 ON 14 JUL 2005

L3 FILE 'HCAPLUS' ENTERED AT 11:06:09 ON 14 JUL 2005  
TRA L1 1- RN : 3 TERMS

L4 FILE 'REGISTRY' ENTERED AT 11:06:12 ON 14 JUL 2005  
3 SEA ABB=ON PLU=ON L3  
SAVE TEMP L4 KAN699REGAPP/A

FILE 'STNGUIDE' ENTERED AT 11:06:39 ON 14 JUL 2005

L5 FILE 'LREGISTRY' ENTERED AT 11:06:57 ON 14 JUL 2005  
STRUCTURE UPLOADED  
L6 STR L5

FILE 'REGISTRY' ENTERED AT 11:11:55 ON 14 JUL 2005  
D SCAN L4

L7 8 SEA SSS SAM L6  
D SCAN  
D QUE STAT

L8 312 SEA SSS FUL L6  
SAVE TEMP L8 KAN699PSET1/A

FILE 'STNGUIDE' ENTERED AT 11:15:01 ON 14 JUL 2005  
D SAVED

L9 FILE 'REGISTRY' ENTERED AT 11:16:57 ON 14 JUL 2005  
1 SEA ABB=ON PLU=ON L8 AND L4

FILE 'STNGUIDE' ENTERED AT 11:17:05 ON 14 JUL 2005

L10 FILE 'REGISTRY' ENTERED AT 11:18:53 ON 14 JUL 2005  
ANALYZE PLU=ON L8 1- LC : 35 TERMS  
D

FILE 'HCAPLUS' ENTERED AT 11:20:23 ON 14 JUL 2005

FILE 'REGISTRY' ENTERED AT 11:20:25 ON 14 JUL 2005  
D QUE STAT L9  
D IDERL L9

FILE 'STNGUIDE' ENTERED AT 11:21:05 ON 14 JUL 2005



FILE 'LREGISTRY' ENTERED AT 11:37:24 ON 14 JUL 2005  
L\*\*\* DEL STR L6  
L11 STR L6

FILE 'REGISTRY' ENTERED AT 11:44:53 ON 14 JUL 2005  
L12 3 SEA SUB=L8 SSS SAM L11  
D SCAN

FILE 'STNGUIDE' ENTERED AT 11:45:25 ON 14 JUL 2005

FILE 'LREGISTRY' ENTERED AT 11:56:12 ON 14 JUL 2005  
L13 STR L11

FILE 'REGISTRY' ENTERED AT 11:59:06 ON 14 JUL 2005  
L14 3 SEA SUB=L8 SSS SAM L13  
D QUE L11  
L15 135 SEA SUB=L8 SSS FUL L13  
SAVE TEMP L15 KAN699RSET1/A  
L16 1 SEA ABB=ON PLU=ON L15 AND L4  
L17 177 SEA ABB=ON PLU=ON L8 NOT L15

FILE 'STNGUIDE' ENTERED AT 12:06:58 ON 14 JUL 2005  
D SAVED

FILE 'ZREGISTRY' ENTERED AT 12:19:39 ON 14 JUL 2005

FILE 'REGISTRY' ENTERED AT 12:20:43 ON 14 JUL 2005  
L18 ANALYZE PLU=ON L15 1- LC : 35 TERMS  
D  
D COST

FILE 'STNGUIDE' ENTERED AT 12:21:47 ON 14 JUL 2005

FILE 'REGISTRY' ENTERED AT 12:22:00 ON 14 JUL 2005  
L19 0 SEA ABB=ON PLU=ON L15 AND L1  
L20 1 SEA ABB=ON PLU=ON L15 AND L4

FILE 'STNGUIDE' ENTERED AT 12:22:15 ON 14 JUL 2005

FILE 'HCAPLUS' ENTERED AT 12:23:28 ON 14 JUL 2005  
L21 433 SEA ABB=ON PLU=ON L15  
L22 337 SEA ABB=ON PLU=ON L21 AND (AY<2002 OR PY<2002 OR PRY<2002)

FILE 'STNGUIDE' ENTERED AT 12:24:18 ON 14 JUL 2005

FILE 'HCAPLUS' ENTERED AT 12:28:10 ON 14 JUL 2005  
L23 QUE ABB=ON PLU=ON (CA OR ?CALCIUM?) (2A) (?CHANNEL? OR  
?SIGNAL?)  
L24 303 SEA ABB=ON PLU=ON L21 AND L23  
L25 136 SEA ABB=ON PLU=ON L15 (L) L23  
L26 108 SEA ABB=ON PLU=ON L25 AND (AY<2002 OR PY<2002 OR PRY<2002)

FILE 'REGISTRY' ENTERED AT 12:30:33 ON 14 JUL 2005  
L27 134 SEA ABB=ON PLU=ON L15 NOT L16  
SAVE TEMP L27 KAN699RSET2/A

FILE 'STNGUIDE' ENTERED AT 12:31:14 ON 14 JUL 2005  
D SAVED

FILE 'HCAPLUS' ENTERED AT 12:31:40 ON 14 JUL 2005

L28 69 SEA ABB=ON PLU=ON L27  
L29 7 SEA ABB=ON PLU=ON 116644-53-2D?  
L30 76 SEA ABB=ON PLU=ON L28 OR L29  
L31 21 SEA ABB=ON PLU=ON L30 (L) L23  
L32 73 SEA ABB=ON PLU=ON L30 AND (AY<2002 OR PY<2002 OR PRY<2002)  
L33 20 SEA ABB=ON PLU=ON L31 AND (AY<2002 OR PY<2002 OR PRY<2002)  
L34 1 SEA ABB=ON PLU=ON L31 AND L1  
D SCAN L31

FILE 'STNGUIDE' ENTERED AT 12:34:02 ON 14 JUL 2005

FILE 'HCAPLUS' ENTERED AT 12:42:33 ON 14 JUL 2005

L35 QUE ABB=ON PLU=ON ?HYPERTENS? OR ?ANGINA? OR ?ISCHEM? OR  
?ARRHYTHM? OR ?CARDIAC? OR ?CARDIO? OR HEART  
D QUE L26  
L36 70 SEA ABB=ON PLU=ON L25 AND (?HYPERTENS?/OBI OR ?ANGINA?/OBI  
OR ?ISCHEM?/OBI OR ?ARRHYTHM?/OBI OR ?CARDIAC?/OBI OR ?CARDIO?/  
OBI OR HEART/OBI)  
L37 58 SEA ABB=ON PLU=ON L26 AND L36  
L38 152 SEA ABB=ON PLU=ON L15 (L) L35  
L39 47 SEA ABB=ON PLU=ON L25 AND L38  
L40 59 SEA ABB=ON PLU=ON L31 OR L39  
D QUE  
L41 53 SEA ABB=ON PLU=ON L40 AND (AY<2002 OR PY<2002 OR PRY<2002)

FILE 'STNGUIDE' ENTERED AT 12:45:58 ON 14 JUL 2005

FILE 'HCAPLUS' ENTERED AT 12:47:38 ON 14 JUL 2005

SAVE TEMP L41 KAN699HCA1B/A

FILE 'STNGUIDE' ENTERED AT 12:47:53 ON 14 JUL 2005

D SAVED

FILE 'USPATFULL, USPAT2' ENTERED AT 12:49:22 ON 14 JUL 2005

L42 58 SEA ABB=ON PLU=ON L15  
L43 49 SEA ABB=ON PLU=ON L42 AND (L23/BI,IT,ST,CC OR L35/BI,IT,ST,CC  
)  
L44 38 SEA ABB=ON PLU=ON L42 AND (L23/IT,ST,CC OR L35/IT,ST,CC)  
L45 33 SEA ABB=ON PLU=ON L44 AND (AY<2002 OR PY<2002 OR PRY<2002)  
SAVE TEMP L45 KAN699USP1B/A

FILE 'STNGUIDE' ENTERED AT 12:52:09 ON 14 JUL 2005

D SAVED

FILE 'TOXCENTER' ENTERED AT 12:53:17 ON 14 JUL 2005

L46 326 SEA ABB=ON PLU=ON L15  
L47 229 SEA ABB=ON PLU=ON L46 AND L23  
L48 164 SEA ABB=ON PLU=ON L47 AND L35  
L49 12 SEA ABB=ON PLU=ON L48 AND REVIEW/DT  
L50 36 SEA ABB=ON PLU=ON L27  
L51 35 SEA ABB=ON PLU=ON L50 AND (PY<2002 OR MY<2002)  
L52 47 SEA ABB=ON PLU=ON L49 OR L51  
SAVE TEMP L52 KAN699TOX1B/A

FILE 'STNGUIDE' ENTERED AT 12:57:26 ON 14 JUL 2005

D SAVED

FILE 'REGISTRY' ENTERED AT 12:58:01 ON 14 JUL 2005

E RO 40-5967/CN

L53 1 SEA ABB=ON PLU=ON "RO 40-5967"/CN

## D SCAN

FILE 'STNGUIDE' ENTERED AT 13:00:35 ON 14 JUL 2005

FILE 'MEDLINE, BIOSIS, PASCAL, JICST-EPLUS, CANCERLIT, DRUGU, SCISEARCH'  
ENTERED AT 13:00:55 ON 14 JUL 2005

FILE 'REGISTRY' ENTERED AT 13:01:10 ON 14 JUL 2005

L54 SET SMARTSELECT ON  
SEL PLU=ON L15 1- CHEM : 154 TERMS  
SET SMARTSELECT OFF

FILE 'MEDLINE, BIOSIS, PASCAL, JICST-EPLUS, CANCERLIT, DRUGU, SCISEARCH'  
ENTERED AT 13:01:21 ON 14 JUL 2005

L55 2569 SEA ABB=ON PLU=ON L54  
L56 978 SEA ABB=ON PLU=ON L55 (15A) L23  
L57 925 SEA ABB=ON PLU=ON L55 (10A) L23  
L58 1558 SEA ABB=ON PLU=ON L55 (L) L35  
L59 981 SEA ABB=ON PLU=ON L55 (10A) L35  
L60 483 SEA ABB=ON PLU=ON L57 AND L59  
L61 269 DUP REM L60 (214 DUPLICATES REMOVED)  
ANSWERS '1-74' FROM FILE MEDLINE  
ANSWERS '75-215' FROM FILE BIOSIS  
ANSWERS '216-227' FROM FILE PASCAL  
ANSWER '228' FROM FILE JICST-EPLUS  
ANSWERS '229-258' FROM FILE DRUGU  
ANSWERS '259-269' FROM FILE SCISEARCH  
L62 229 SEA ABB=ON PLU=ON L61 AND L23/IT,ST,CT,CC,TI  
L63 246 SEA ABB=ON PLU=ON L61 AND L35/IT,ST,CT,CC,TI  
L64 211 SEA ABB=ON PLU=ON L62 AND L63  
L65 142 SEA ABB=ON PLU=ON L64 AND (AY<2002 OR PY<2002 OR PRY<2002 OR  
MY<2002)  
D QUE L27  
D QUE L35  
L66 97 SEA ABB=ON PLU=ON L65 AND (?HYPERTENS? OR ?ANGINA? OR  
?ISCHEM? OR ?ARRHYTH? OR ?ANTIHYPERTENS? OR ?ANTIANGINA? OR  
?ANTIISCHEM? OR ?ANTIARRHYTHM?)  
L67 83 SEA ABB=ON PLU=ON L65 AND (?HYPERTENS? OR ?ANGINA? OR  
?ISCHEM? OR ?ARRHYTH? OR ?ANTIHYPERTENS? OR ?ANTIANGINA? OR  
?ANTIISCHEM? OR ?ANTIARRHYTHM?)/IT,ST,CC,CT,TI  
SAVE TEMP L67 KAN699MUL1B/A  
D SAVED

FILE 'EMBASE' ENTERED AT 13:24:19 ON 14 JUL 2005

FILE 'REGISTRY' ENTERED AT 13:24:30 ON 14 JUL 2005

L68 SET SMARTSELECT ON  
SEL ABB=ON PLU=ON L15 1- CHEM : 154 TERMS  
SET SMARTSELECT OFF

FILE 'EMBASE' ENTERED AT 13:24:40 ON 14 JUL 2005

L69 935 SEA ABB=ON PLU=ON L68  
L70 511 SEA ABB=ON PLU=ON L69 AND L23  
L71 259 SEA ABB=ON PLU=ON L70 AND (?HYPERTENS? OR ?ANGINA? OR  
?ISCHEM? OR ?ARRHYTH? OR ?ANTIHYPERTENS? OR ?ANTIANGINA? OR  
?ANTIISCHEM? OR ?ANTIARRHYTHM?)  
L72 259 SEA ABB=ON PLU=ON L70 AND L71  
L73 198 SEA ABB=ON PLU=ON L70 AND (?HYPERTENS? OR ?ANGINA? OR  
?ISCHEM? OR ?ARRHYTH? OR ?ANTIHYPERTENS? OR ?ANTIANGINA? OR  
?ANTIISCHEM? OR ?ANTIARRHYTHM?)/CT

L74 198 SEA ABB=ON PLU=ON L72 AND L73  
L75 176 SEA ABB=ON PLU=ON L74/MAJ  
D SCAN  
D TRI 1-5  
L76 148 SEA ABB=ON PLU=ON L75 AND (PY<2002 OR MY<2002)  
D QUE  
L77 47 SEA ABB=ON PLU=ON L70 AND ((CA/CT OR ?CALCIUM?/CT) (2A) (?CHANN  
EL?/CT OR ?SIGNAL?/CT))  
D TRI 1-3  
L78 8 SEA ABB=ON PLU=ON L74 AND L77  
L79 39 SEA ABB=ON PLU=ON L77/MAJ  
L80 24 SEA ABB=ON PLU=ON L79 AND (PY<2002 OR MY<2002)  
SAVE TEMP L80 KAN699EMB1B/A  
D TRI 1-5  
L81 6 SEA ABB=ON PLU=ON L80 AND L71  
L82 6 SEA ABB=ON PLU=ON L80 AND (?HYPERTENS?/CT OR ?ANGINA?/CT OR  
?ISCHEM?/CT OR ?ARRHYTHM?/CT OR ?CARDIAC?/CT OR ?CARDIO?/CT OR  
HEART/CT)  
D TRI 1-6  
SAVE TEMP L82 KAN699EMB2B/A

FILE 'STNGUIDE' ENTERED AT 13:33:37 ON 14 JUL 2005

D SAVED

FILE 'WPIX' ENTERED AT 13:35:29 ON 14 JUL 2005

E MIBEFRADIL/CN

E RO 40-5967/CN

E RO-40

E RO-40/CN

L83 1 SEA ABB=ON PLU=ON MIBEFRADIL/CN OR RO-40-5967/CN  
D 1-2

SELECT L83 1- SY

L84 43 SEA ABB=ON PLU=ON (MIBEFRADIL/BIX OR POSICOR/BIX OR RO-40-596  
7/BIX)

FILE 'STNGUIDE' ENTERED AT 13:37:36 ON 14 JUL 2005

FILE 'WPIX' ENTERED AT 13:39:48 ON 14 JUL 2005

L85 16553 SEA ABB=ON PLU=ON A61P009?/IPC

L86 44034 SEA ABB=ON PLU=ON (B14-F01? OR C14-F01? OR B14-F02? OR  
C14-F02?)/MC

L87 30 SEA ABB=ON PLU=ON L84 AND (L85 OR L86)

L88 18 SEA ABB=ON PLU=ON L87 AND ((CA/BIX OR ?CALCIUM?/BIX) (2A) (?CHA  
NNEL?/BIX OR ?SIGNAL?/BIX))

L89 17 SEA ABB=ON PLU=ON L87 AND (AY<2002 OR PY<2002 OR PRY<2002)

L90 9 SEA ABB=ON PLU=ON L88 AND L89

SAVE TEMP L90 KAN699WPI1B/A

FILE 'STNGUIDE' ENTERED AT 13:58:12 ON 14 JUL 2005

D SAVED

FILE 'HCAPLUS, MEDLINE, BIOSIS, PASCAL, JICST-EPLUS, EMBASE, CANCERLIT,  
DRUGU, SCISEARCH, WPIX, CONF, CONFSCI' ENTERED AT 14:00:10 ON 14 JUL 2005

L91 196 SEA ABB=ON PLU=ON DRUZGALA, P?/AU

L92 1696 SEA ABB=ON PLU=ON MILNER, P?/AU

L93 1153 SEA ABB=ON PLU=ON PFISTER, J?/AU

L94 82454 SEA ABB=ON PLU=ON ZHANG, X?/AU

L95 490 SEA ABB=ON PLU=ON (L91 OR L92 OR L93 OR L94) AND L23

D QUE L90

L96 3 SEA ABB=ON PLU=ON L95 AND (?MIBEFRADIL? OR ?POSICOR? OR

(RO(1W) 40(1W) 5967))  
L97 3 SEA ABB=ON PLU=ON L95 AND ARYX/CS,SO,PA  
L98 3 SEA ABB=ON PLU=ON (L96 OR L97)  
L99 2 DUP REM L98 (1 DUPLICATE REMOVED)  
ANSWER '1' FROM FILE HCAPLUS  
ANSWER '2' FROM FILE BIOSIS  
SAVE TEMP L99 KAN699MULINV/A  
D QUE  
L100 3 SEA ABB=ON PLU=ON (L91 OR L92 OR L93 OR L94) AND (?MIBEFRADIL  
? OR ?POSICOR? OR (RO(1W) 40(1W) 5967))  
L101 3 SEA ABB=ON PLU=ON L99 OR L100  
L102 2 DUP REM L101 (1 DUPLICATE REMOVED)  
ANSWER '1' FROM FILE HCAPLUS  
ANSWER '2' FROM FILE BIOSIS  
SAVE TEMP L102 KAN699MULINV/A  
D SAVED

FILE 'STNGUIDE' ENTERED AT 14:06:48 ON 14 JUL 2005

FILE 'REGISTRY' ENTERED AT 14:08:35 ON 14 JUL 2005

FILE 'LREGISTRY' ENTERED AT 14:08:39 ON 14 JUL 2005

FILE 'ZCAPLUS' ENTERED AT 14:08:42 ON 14 JUL 2005

FILE 'HCAPLUS' ENTERED AT 14:08:44 ON 14 JUL 2005

FILE 'MEDLINE' ENTERED AT 14:08:55 ON 14 JUL 2005

FILE 'BIOSIS' ENTERED AT 14:08:59 ON 14 JUL 2005

FILE 'PASCAL' ENTERED AT 14:09:02 ON 14 JUL 2005

FILE 'JICST-EPLUS' ENTERED AT 14:09:05 ON 14 JUL 2005

FILE 'EMBASE' ENTERED AT 14:09:08 ON 14 JUL 2005

FILE 'CANCERLIT' ENTERED AT 14:09:12 ON 14 JUL 2005

FILE 'DRUGU' ENTERED AT 14:09:15 ON 14 JUL 2005

FILE 'SCISEARCH' ENTERED AT 14:09:19 ON 14 JUL 2005

FILE 'WPIX' ENTERED AT 14:09:23 ON 14 JUL 2005

FILE 'CONF' ENTERED AT 14:09:27 ON 14 JUL 2005

FILE 'CONFSCI' ENTERED AT 14:09:32 ON 14 JUL 2005

FILE 'USPATFULL' ENTERED AT 14:09:35 ON 14 JUL 2005

FILE 'USPAT2' ENTERED AT 14:09:39 ON 14 JUL 2005

FILE 'STNGUIDE' ENTERED AT 14:09:51 ON 14 JUL 2005

D QUE STAT L41

D QUE STAT L15

D QUE L41

D QUE NOS L45

D QUE NOS L90

D QUE NOS L82

D QUE NOS L52  
D QUE NOS L67

FILE 'HCAPLUS, USPATFULL, USPAT2, WPIX, EMBASE, TOXCENTER, MEDLINE, BIOSIS, PASCAL, DRUGU, SCISEARCH' ENTERED AT 14:13:01 ON 14 JUL 2005  
L103 198 DUP REM L41 L45 L90 L82 L52 L67 (33 DUPLICATES REMOVED)

ANSWERS '1-53' FROM FILE HCAPLUS  
ANSWERS '54-79' FROM FILE USPATFULL  
ANSWERS '80-85' FROM FILE WPIX  
ANSWERS '86-90' FROM FILE EMBASE  
ANSWERS '91-131' FROM FILE TOXCENTER  
ANSWERS '132-140' FROM FILE MEDLINE  
ANSWERS '141-172' FROM FILE BIOSIS  
ANSWERS '173-177' FROM FILE PASCAL  
ANSWERS '178-195' FROM FILE DRUGU  
ANSWERS '196-198' FROM FILE SCISEARCH

FILE 'STNGUIDE' ENTERED AT 14:13:48 ON 14 JUL 2005

FILE 'HCAPLUS, USPATFULL, TOXCENTER, MEDLINE, BIOSIS, PASCAL, DRUGU, SCISEARCH, EMBASE, WPIX' ENTERED AT 14:14:02 ON 14 JUL 2005  
D IBIB ED AB HITIND HITSTR

FILE 'STNGUIDE' ENTERED AT 14:14:03 ON 14 JUL 2005

FILE 'HCAPLUS, USPATFULL, TOXCENTER, MEDLINE, BIOSIS, PASCAL, DRUGU, SCISEARCH, EMBASE, WPIX' ENTERED AT 14:14:22 ON 14 JUL 2005  
D IBIB ED AB HITIND HITSTR 2-53

FILE 'STNGUIDE' ENTERED AT 14:14:33 ON 14 JUL 2005

FILE 'HCAPLUS, USPATFULL, TOXCENTER, MEDLINE, BIOSIS, PASCAL, DRUGU, SCISEARCH, EMBASE, WPIX' ENTERED AT 14:17:04 ON 14 JUL 2005  
D IBIB AB KWIC HITSTR 54-79

FILE 'STNGUIDE' ENTERED AT 14:17:19 ON 14 JUL 2005

FILE 'HCAPLUS, USPATFULL, TOXCENTER, MEDLINE, BIOSIS, PASCAL, DRUGU, SCISEARCH, EMBASE, WPIX' ENTERED AT 14:19:52 ON 14 JUL 2005  
D IALL ABEQ TECH ABEX 80-85

FILE 'STNGUIDE' ENTERED AT 14:19:56 ON 14 JUL 2005

FILE 'HCAPLUS, USPATFULL, TOXCENTER, MEDLINE, BIOSIS, PASCAL, DRUGU, SCISEARCH, EMBASE, WPIX' ENTERED AT 14:20:55 ON 14 JUL 2005  
D IBIB ED AB HITIND 86-

FILE 'STNGUIDE' ENTERED AT 14:22:00 ON 14 JUL 2005  
D QUE L102

FILE 'HCAPLUS, BIOSIS' ENTERED AT 14:23:01 ON 14 JUL 2005  
D IBIB ED AB L102

FILE 'STNGUIDE' ENTERED AT 14:23:01 ON 14 JUL 2005

FILE 'HCAPLUS, BIOSIS' ENTERED AT 14:23:06 ON 14 JUL 2005  
D IBIB ED AB L102 2

FILE 'STNGUIDE' ENTERED AT 14:23:07 ON 14 JUL 2005

FILE 'STNGUIDE' ENTERED AT 14:23:18 ON 14 JUL 2005

D QUE STAT L8  
D QUE STAT L15  
D QUE NOS L41  
D QUE L45  
D QUE L90  
D QUE L52  
D QUE L82  
D QUE NOS L67  
D QUE L102

FILE HOME

FILE STNGUIDE

FILE CONTAINS CURRENT INFORMATION.

LAST RELOADED: Jul 8, 2005 (20050708/UP).

FILE HCAPLUS

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FILE COVERS 1907 - 14 Jul 2005 VOL 143 ISS 3

FILE LAST UPDATED: 13 Jul 2005 (20050713/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE WPIX

FILE LAST UPDATED: 12 JUL 2005 <20050712/UP>

MOST RECENT DERWENT UPDATE: 200544 <200544/DW>

DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,  
PLEASE VISIT:  
[http://www.stn-international.de/training\\_center/patents/stn\\_guide.pdf](http://www.stn-international.de/training_center/patents/stn_guide.pdf) <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE  
<http://thomsonderwent.com/coverage/latestupdates/> <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER  
GUIDES, PLEASE VISIT:  
<http://thomsonderwent.com/support/userguides/> <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT  
DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX  
FIRST VIEW - FILE WPIFV.  
FOR FURTHER DETAILS: <http://www.thomsonderwent.com/dwpifv> <<<

>>> THE CPI AND EPI MANUAL CODES HAVE BEEN REVISED FROM UPDATE 200501.

PLEASE CHECK:  
<http://thomsonderwent.com/support/dwpioref/reftools/classification/code-rev>  
FOR DETAILS. <<<

#### FILE REGISTRY

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 13 JUL 2005 HIGHEST RN 854992-86-2

DICTIONARY FILE UPDATES: 13 JUL 2005 HIGHEST RN 854992-86-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

```
*****
*
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005. A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*
*****
```

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:  
<http://www.cas.org/ONLINE/DBSS/registryss.html>

#### FILE LREGISTRY

LREGISTRY IS A STATIC LEARNING FILE

NEW CAS INFORMATION USE POLICIES, ENTER HELP USAGETERMS FOR DETAILS.

#### FILE ZREGISTRY

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 13 JUL 2005 HIGHEST RN 854992-86-2

DICTIONARY FILE UPDATES: 13 JUL 2005 HIGHEST RN 854992-86-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

```
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*
* The CA roles and document type information have been removed from *
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* available and contains the CA role and document type information. *
*
*****
```



\*\*\*\*\*

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:

<http://www.cas.org/ONLINE/DBSS/zregistryss.html>

FILE USPATFULL

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 12 Jul 2005 (20050712/PD)

FILE LAST UPDATED: 12 Jul 2005 (20050712/ED)

HIGHEST GRANTED PATENT NUMBER: US6918136

HIGHEST APPLICATION PUBLICATION NUMBER: US2005150027

CA INDEXING IS CURRENT THROUGH 12 Jul 2005 (20050712/UPCA)

ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 12 Jul 2005 (20050712/PD)

REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2005

USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2005

>>> USPAT2 is now available. USPATFULL contains full text of the <<<  
>>> original, i.e., the earliest published granted patents or <<<  
>>> applications. USPAT2 contains full text of the latest US <<<  
>>> publications, starting in 2001, for the inventions covered in <<<  
>>> USPATFULL. A USPATFULL record contains not only the original <<<  
>>> published document but also a list of any subsequent <<<  
>>> publications. The publication number, patent kind code, and <<<  
>>> publication date for all the US publications for an invention <<<  
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<  
>>> records and may be searched in standard search fields, e.g., /PN, <<<  
>>> /PK, etc. <<<

>>> USPATFULL and USPAT2 can be accessed and searched together <<<  
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<  
>>> enter this cluster. <<<  
>>> <<<  
>>> Use USPATALL when searching terms such as patent assignees, <<<  
>>> classifications, or claims, that may potentially change from <<<  
>>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE USPAT2

FILE COVERS 2001 TO PUBLICATION DATE: 12 Jul 2005 (20050712/PD)

FILE LAST UPDATED: 12 Jul 2005 (20050712/ED)

HIGHEST GRANTED PATENT NUMBER: US2004225788

HIGHEST APPLICATION PUBLICATION NUMBER: US2005150026

CA INDEXING IS CURRENT THROUGH 12 Jul 2005 (20050712/UPCA)

ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 12 Jul 2005 (20050712/PD)

REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2005

USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2005

USPAT2 is a companion file to USPATFULL. USPAT2 contains full text of the latest US publications, starting in 2001, for the inventions covered in USPATFULL. USPATFULL contains full text of the original published US patents from 1971 to date and the original applications from 2001. In addition, a USPATFULL record for an invention contains a complete list of publications that may be searched in standard search fields, e.g., /PN, /PK, etc.

USPATFULL and USPAT2 can be accessed and searched together through the new cluster USPATALL. Type FILE USPATALL to enter this cluster.

Use USPATALL when searching terms such as patent assignees, classifications, or claims, that may potentially change from the earliest to the latest publication.

#### FILE TOXCENTER

FILE COVERS 1907 TO 12 Jul 2005 (20050712/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TOXCENTER has been enhanced with new files segments and search fields. See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary. See <http://www.nlm.nih.gov/mesh/> and [http://www.nlm.nih.gov/pubs/techbull/nd04/nd04\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html) for a description of changes.

#### FILE MEDLINE

FILE LAST UPDATED: 13 JUL 2005 (20050713/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow prompt (=>). See also:

<http://www.nlm.nih.gov/mesh/>  
[http://www.nlm.nih.gov/pubs/techbull/nd04/nd04\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html)

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

#### FILE BIOSIS

FILE COVERS 1969 TO DATE.

CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 8 July 2005 (20050708/ED)

FILE RELOADED: 19 October 2003.

#### FILE PASCAL

FILE LAST UPDATED: 11 JUL 2005 <20050711/UP>

FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE  
IN THE BASIC INDEX (/BI) FIELD <<<

FILE JICST-EPLUS  
FILE COVERS 1985 TO 11 JUL 2005 (20050711/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED TERM (/CT) THESAURUS RELOAD.

FILE CANCERLIT  
FILE COVERS 1963 TO 15 Nov 2002 (20021115/ED)

On July 28, 2002, CANCERLIT was reloaded. See HELP RLOAD for details.

CANCERLIT thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE DRUGU  
FILE LAST UPDATED: 13 JUL 2005 <20050713/UP>  
>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> FILE COVERS 1983 TO DATE <<<  
>>> THESAURUS AVAILABLE IN /CT <<<

FILE SCISEARCH  
FILE COVERS 1974 TO 8 Jul 2005 (20050708/ED)

FILE EMBASE  
FILE COVERS 1974 TO 7 Jul 2005 (20050707/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE CONF  
FILE LAST UPDATED: 8 JUL 2005 <20050708/UP>  
FILE COVERS 1976 TO DATE.

FILE CONFSCI  
FILE COVERS 1973 TO 25 May 2005 (20050525/ED)

FILE ZCAPLUS

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FILE COVERS 1907 - 14 Jul 2005 VOL 143 ISS 3  
FILE LAST UPDATED: 13 Jul 2005 (20050713/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate  
substance identification.

=>